Cognitive Behavioural Therapy (CBT) for Schizophrenia: A Meta-Analysis

Gemma Holton

BA (Hons)

A report submitted in partial requirement for the degree of Master of Psychology (Clinical) at the University of Tasmania

October 2015

I declare that this research report is my own work, and that, to the best of my knowledge and belief, it does not contain material from published sources without acknowledgement, nor does it contain material which has been accepted for the award for any other higher degree or graduate diploma in any university.

Gemma Holton

Acknowledgements

I wish to express my thanks to my supervisor Dr Bethany Wootton for her considerate support throughout this project. I am extremely grateful for all the practical advice and continual support and encouragement she gave. Dr Wootton encouraged me to complete my thesis in an area of my interest and never expressed any doubt in my ability. Her methodical and consistent approach, patience and valuable advice are truly appreciated.

I thank the staff of RFT who understood my vision when I informed them I was returning to university to complete my Masters in clinical psychology. RFT have been immensely supportive throughout this degree, encouraging me to achieve and share my knowledge, and share my valuable time.

To my family and friends, I would like to say a big thank you for encouraging me to return to university and finish what I began. Thank you for supporting me and understanding how much time was dedicated to completing my studies. A particular thank you to my mother Mary Holton, I would probably have not chosen this path if it was not for your determination for me to finish what I had begun, and your belief in me.

Finally a very special thank you to my sister Tamika. Thank you for all your love, support and words of encouragement throughout the past two years. You were always there to push me on, and believed in me when I didn't always believe in myself. I would have never accomplished it without you.

Table of Contents

Cognitive Behavioural Therapy (CBT) for Schizophrenia: A meta-analysis

Gemma Holton

BA (Hons)

A report submitted in partial requirement for the degree of Master of Psychology (Clinical) at the University of Tasmania

October 2015

Abstract

Background: Despite the effectiveness of pharmacotherapy for the treatment of schizophrenia, up to 60% continue to experience distressing symptoms such as hallucinations or delusions. Adjunctive cognitive behavioural therapy (CBT) is now recommended in many countries. There has been some debate as to whether CBT is effective in reducing the symptoms of schizophrenia. Meta-analyses to date have shown varying results. The aim of this meta-analysis was to examine moderating effects of a) study/trial quality, b) comprehensiveness of the CBT intervention, c) manualized vs. non manualized treatments, d) control group, e) chronicity of presentations of schizophrenia, and f) format of treatment. *Method:* A systematic search of the literature was conducted in PsychInfo, Scopus, Embase and Medline to identify randomized controlled trials reporting on the impact of CBT on positive, negative, global psychopathology and total symptoms and a random-effects meta-analysis was performed. *Results:* 23 studies including 2,639 participants published between 1990 and 2015 were identified. Small and largely non-significant effect sizes were found at post-treatment for total symptoms (g=0.19), negative symptoms (g= 0.12) and global psychopathology (g=0.12),, with a significant but small effect size found for the reduction of positive symptoms (g=0.19). Moderators had little impact overall, with no consistent evidence of quality, comprehensiveness, manualisation, control group, stage of illness or format of treatment moderating effect size for any symptom type. The clinical implications for the use of CBT with this population are discussed.

Schizophrenia is a chronic psychotic disorder that is characterised by a heterogeneous range of positive and negative symptoms that cause a profound disruption in most, if not all aspects of daily life. The disorder has been described in the literature since 1911 and has evolved significantly over time. While the prevalence is low, schizophrenia accounts for a significant financial burden to society. The nature of the disorder, the costs to society and current theoretical and treatment approaches are described below. A meta-analysis of existing cognitive-behavioural treatments for schizophrenia is then conducted, which aims to address some of the limitations of existing meta-analyses in this field.

Definitions, diagnosis and clinical features

Schizophrenia is a psychotic disorder that is characterized by the presence of delusions, hallucinations, disorganized speech, disorganized or catatonic behavior and negative symptoms (APA, 2013). These symptoms must cause a significant impact on functioning and must be present for at least 6 months to warrant diagnosis (APA, 2013). The 12-month prevalence of schizophrenia in Australia is estimated to be less than 1% (AIHW, 2005; AIHW, 2014) and is estimated to be approximately 1% in the USA (Tarrier & Wykes 2004). The DSM-5 criteria for schizophrenia is outlined in Appendix A.

Schizophrenia typically has an onset in late adolescence or early adulthood for men and early to mid-adulthood for women, and tends to persist for the remainder of the lifespan (Riecher-Rossler & Hafner, 2000). The onset of schizophrenia is generally preceded by a period of time whereby the individual may experience, or others may notice, changes in sleep, cognition, perception, and altered communication with others (Yung & McGorry, 1996, Larson, Walker & Compton, 2010). The course of schizophrenia is often changing, with periods of recovery or

remission followed by relapse (Harrow et al., 1997), however approximately one third of patients demonstrate a chronic and stable course with limited or no periods of remission (Ciompi, 1980).

In the literature psychotic symptoms are often divided into 'positive' and 'negative' symptoms. Positive symptoms are symptoms that are present in addition, or above, normal functioning and include delusions, hallucinations, disorganized speech and disorganized behavior. Negative symptoms are described as an 'absence' or decline in normal functioning. Often the negative symptoms precede the onset of the positive symptoms (Hafner et al., (1994), however, it is the positive symptoms that often leads to the diagnosis of schizophrenia (Tsuang et al., 2000).

Positive symptoms. Delusions occur in 65% of individuals with schizophrenia (Breier & Berg, 1999) and are defined as false beliefs that are held despite lack of evidence (APA, 2013). Delusions can come in many forms and the most commonly occurring delusions in schizophrenia are outlined in Table 1. Persecutory delusions are the most common, and occur in approximately 93% of the schizophrenic population (AlFaraj et al., 2006). Hallucinations also occur frequently in individuals with schizophrenia with auditory hallucinations being the most common (75% of patients), followed by visual hallucinations (34% of patients) and somatic hallucinations (29% of patients) (Bauer et al., 2011). Tactile, olfactory, and gustatory hallucinations occur less often (1.3-6.6% of patients) (Bauer et al., 2011).

Table 1

Type and description of common delusions

Delusion	Description
Persecutory	A belief that one is being harassed, or might be harmed

Jealousy	A belief that an individual's spouse or partner are being unfaithful
Passivity/Control	A belief that one or one's will is being controlled by something or someone, or that they can control others' will
Thought insertion	A belief that thoughts are being intentionally inserted into one's mind
Thought withdrawal	A belief that thoughts are being intentionally being removed from one's mind
Thought broadcasting	A belief that one's thoughts can be seen, heard or understood by others without those thoughts being spoken
Grandiose	A belief that one is of extreme importance or have extreme power
Reference	A belief that gestures and words of others are directed at them
Religious	Misguided beliefs around one's relationship with God, or that they have been given special powers by God, or that they are God.
Somatic	Beliefs that one has a physical condition, or erroneous beliefs about parts of one's body.
Erotomanic	A belief that someone is romantically or sexually involved or in love with him/her
Guilt or Sin	A feeling of remorse or guilt that is unfounded

Disorganized speech, also known as formal thought disorder occurs in approximately 65% of individuals with schizophrenia (AlFaraj et al., 2006). This involves a heterogeneous range of symptoms and can include derailment,

tangentiality, incoherence, illogicality, circumstantiality, pressured speech, distractible speech and clang associations (AlFaraj et al., 2006; Rule, 2005; Harvey et al., 1997). Descriptions and prevalence rates for these symptoms are outlined in Table 2. Disorganised behaviours that are seen in schizophrenia include bizarre clothing or appearance, bizarre social or sexual behaviour, bizarre aggressive or agitated behaviour, and bizarre repetitive or stereotyped behaviours (Andreason, 1995). These behaviours are the most commonly observed symptom for general practitioners seeing first episode psychosis (O'Callaghan et al., 2006).

Negative symptoms. The negative symptoms in schizophrenia are also heterogeneous. The most easily observed are the symptoms that could be termed as blunting of affect. This includes unchanging facial expression, decreased spontaneous movements, lack of gesturing, poor eye contact, and lack of vocal inflections. Other negative symptoms include poverty of speech (short responses and minimal elaborations when speaking) and poverty of speech content (lack or reduction of quality of speech), blocking (a sudden inability to complete a sentence, or recall what that sentence was), poor grooming and hygiene, displays of anhedonia, diminished want or need for social relationships and inattentiveness. Approximately 57% of schizophrenia patients experience at least one negative symptom (Bobes et al., 2010).

Table 2

Type and description of positive formal thought disorder symptoms

Symptom	Description	Prevalence of Symptom

Derailment	jumping from one topic to another unrelated topic mid-sentence	50%
Tangentiality	digressing from the topic of conversation	55%
Incoherence	words that are strung together in ways that do not make logical sense	22%
Illogicality	conclusions are formed or arrived at that do not make logical sense	Not provided
Circumstantiality	a difficulty in separating relevant from irrelevant information when describing an event	33%
Pressured Speech	speaking rapidly, motivated by an urgency that is not observable by others, and often hard to understand	21%
Distractible Speech	a change in subject in response to a stimulus	18%
Clang Associations	grouping words together based on sound, rather than meaning	3%

Note. All prevalence rates were obtained from Alfaraj et al, 2006

Distress, Functioning and Comorbidity in Schizophrenia

Schizophrenia has severe and long-lasting impacts on daily functioning, including impairment in ability to attend to household tasks or self-care, or interact in reciprocal relationships with others (Ursano et al, 2004). It is estimated that up to

10% of individuals with schizophrenia will complete suicide (Dickerson & Lehman, 2011) and despite the low prevalence rate, schizophrenia accounts for 20 % of all psychiatric admissions (AIHW 2001). The economic burden of schizophrenia in Australia is significant, resulting in direct costs of $661 million and indirect costs of $722 million (SANE, 2002). Estimates of employment for those with schizophrenia are low (4-27%) when compared to the general population (90%) (Marwaha & Johnson, 2004). Comorbidity with other disorders is common in schizophrenia and the most commonly co-occurring disorders include mood, anxiety and related disorders, and substance use disorders (Volkow, 2009).

Etiological/Risk factors

Despite decades of research into the cause of schizophrenia, to date there is still no clear factors that are common to all experiences of the disease (Walker et al., 2004). The most common theories on the cause or risk of development of schizophrenia include those related to genetics, prenatal and postnatal factors, structural and functional abnormalities of the brain, neurotransmitter models, and environmental models. These are outlined briefly below.

Genetics. Numerous studies now demonstrate the genetic link in schizophrenia. For example, in a review of twin, adoption and family studies, Cardno & Gottesman (2000) found that monozygotic twins had the highest concordance rate (25-50%), followed by dizygotic twins (10-15%) and the development of schizophrenia became more distant from first degree to second degree relatives, suggesting a highly genetic component to the disorder. Additionally, adoption studies often examine rates of schizophrenia amongst biological and non-biological families of adoptees with the illness and have found a higher incidence of schizophrenia amongst parents and offspring in the biological family of the adoptee

with the illness, compared to the parents and relatives that reared them (Tienari et sl., 2003). In a multistage genome-wide association study 22 genomic regions were found to be linked to schizophrenia (Ripke et al., 2013). Despite the gains made in this field, there are several limitations to this research. For instance, there seems to be no evidence that genetic vulnerability is specific to schizophrenia. For instance, Potash et al. (2001) found that there is significant overlap between schizophrenia and bipolar illnesses and argue that the presentation will take the form of one illness or another depending on other risk factors that may be inherited or acquired. Additionally, research has not yet elucidated whether the genetic vulnerability exists for all those who suffer from schizophrenia, and therefore some cases could be due to environmental risk factors (Walker et al., 2004). Several gene expression and association studies are finding promising, but not conclusive results for links with some signaling pathway, genetic variations and polymorphisms and call for larger studies (Andrews & Fernandez-Enright, 2015; Bangel et al., 2015; Liu et al., 2015; Sery et al., 2015).

Prenatal and postnatal factors. Others have studied the environmental triggers that affect fetal development and there have been numerous studies that have linked obstetrical complications with the development of schizophrenia (Cannon et al., 2000, McNeil et al., 2000), however effect sizes tend to be small (for example, 0.31; Cannon et al., 2002). The role of maternal infections such as flu epidemics (Brown et al., 2004), prenatal exposure to rubella (Brown et al, 2001), and season of birth (Giezendanner et al., 2013) have also been found to increase the risk development of schizophrenia, and support the ‘dual hit’ hypothesis (Möller, Swanpoel & Harvey, 2015). This hypothesis suggests that a combination of genetics and an early environmental or inflammatory stressor can prime a person to an ‘event’

later in life (such as drug abuse) which leads to the development of schizophrenia (Möller, Swanpoel & Harvey, 2015). Postnatal factors such as brain injury have been linked to the development of schizophrenia, however published literature on this theory is mixed (Molloy et al., 2011). Meta-analyses such as those by Molloy and colleagues (2011) find an increased risk of the development of schizophrenia following a traumatic brain injury (up to 60%), however the lack of prospective studies in this area limit firm conclusions (David & Prince, 2005). Large longitudinal studies will help to elucidate the role of prenatal and postnatal factors on the development of schizophrenia.

Brain abnormality. Imaging studies have revealed enlarged brain ventricles, a decrease in brain volume, and reductions in the size of the hippocampus and thalamus in individuals with schizophrenia compared to controls (Lawrie & Abukmeil, 1998; Schmajuk, 2001; Pearlson et al 1989). Additionally, morphological abnormalities in the left temporal lobe have been discovered compared with controls (Crowe, 1990). However, despite the numerous findings, none of these results have been found to be specific to schizophrenia, or found across all patients with schizophrenia; or could be a consequence of the disease (Walker et al., 2004). Studies at the cellular level have discovered reductions in neuron density as well as abnormalities in their structure and interconnections (Arnold, 1999). Because these cellular abnormalities seem so widespread (Walker, 1994), researchers propose that schizophrenia involves some form of malfunction of neural circuits (Benes, 2000).

Neurotransmitter models. One of the key neurotransmitters linked with schizophrenia is dopamine. The dopamine hypothesis postulates that schizophrenia results from the brain producing too much dopamine (Howes & Kapur, 2009). This hypothesis was developed on the discovery that drugs such as amphetamines, which

increase the amount of dopamine in the brain, can also induce symptoms of schizophrenia (Grace, 1991; Davis et al., 1991). The dopamine hypothesis was further strengthened by the discovery that patients with Parkinson's disease taking L-Dopa to raise their dopamine levels often developed symptoms similar to schizophrenia if their dose was too high. Post mortems (Kestler et al., 2001) have demonstrated an increased density of the neurotransmitter in the striatum of patients with schizophrenia, and positron emission tomography (PET) scans (Lindstrom et al., 1999) have found dopaminergic processes in various mental activities and treatments; further strengthening the dopamine hypothesis. A second neurotransmitter that has more recently been implicated in schizophrenia is glutamate, whereby the blockade of certain glutamate receptors results in the experience of negative symptoms and cognitive impairments (Goff & Coyle, 2001). Gamma-aminobutyric acid (GABA), serotonin, and noradrenaline have also been implicated in the development of schizophrenia (Carlsson et al., 2001) and thus further research is needed to ascertain the role of neurotransmitter systems in schizophrenia.

Environmental factors. Trauma histories are common in those with schizophrenia, and Morgan and Fisher (2007) found that childhood trauma was a risk factor for the later development of psychosis. Stressful life events, such as being raised in institutional settings or dysfunctional home environments have also been found to predict the development of schizophrenia (Walker et al., 2004). Other environmental factors linked with increased likelihood of the development of schizophrenia include cannabis use (adjusted odds ratios 1.41-2.43, Minozzi et al., 2010), growing up in cities (odds ratios 1.05-2.51, Krabbendam & van Os, 2005), or being part of a minority group (effect size 2.9, Cantor-Graae & Selton, 2005). Whilst

none of these factors alone have a definite causal effect in the development of schizophrenia, they may create vulnerability that when linked with other factors, such as genetics, may increase the likelihood of developing schizophrenia (Van Os, Kenis & Rutten, 2010).

Treatments

Pharmacological. Antipsychotic medications are the most commonly prescribed pharmacology in the treatment of schizophrenia (McGorry, 2005) and are the first line treatment in this disorder. Two forms of anti-psychotics are currently used, the older group, called 'typical' anti-psychotics (i.e., chlorpromazine, haloperidol and thioridazine), and the newer group, are called 'atypical' anti-psychotics (i.e., olanzapine, risperidone, clozapine, quetiapine and amisulpride). Typical antipsychotics demonstrate efficacy (McGorry et al., 2003), but often have more side-effects (Miyamoto et al., 2005), especially if used in higher doses. Atypical medications are now the preferred treatment option because of their superior tolerability, probable greater efficacy in relapse prevention, and reduced risk of tardive dyskinesia (Miyamoto et al., 2005). However, despite adequate dosing up to 60% of patients continue to see medication-resistant symptoms (Lindenmayer, 2000), and it is well recognized that antipsychotic medications have a limited effect on negative symptoms (Pilling et al., 2002). Compliance with medications is also a problem with only about 40% of patients being compliant due to issues such as poor insight, negative attitude towards medication, substance use, and poor therapeutic alliance (Lacro et al., 2002). The efficacy of adjunct psychological treatments is therefore of high importance and is the focus of this thesis.

Psychological Treatments. Many clinical guidelines including The Royal Australian and New Zealand College of Psychiatrists (RANZCP), National Institute

for Clinical Excellent (NICE) and World Health Organisation (WHO) recommend cognitive behavioural therapy (CBT) as an adjunct treatment for individuals with a psychotic illness (Buchanan et al., 2010; Killackey et al., 2008; McGorry, 2005; McGorry et al., 2003; NICE, 2014). However, despite CBT being listed as a recommended adjunctive treatment less than a quarter of patients living with a psychotic illness actually receive this form of therapy (Morgan et al., 2011). CBT for psychotic symptoms is generally based on the cognitive-behavioural model of psychosis, which is outlined below.

Morrison's model of psychosis (Morrison, 2001). Morrison's model of psychosis (Figure 1) is heavily drawn from Clark's cognitive model of panic disorder (Clark, 1986). Morrison (2001) proposes that the intrusions seen in schizophrenia are normal and distress occurs when intrusions are misinterpreted as being dangerous. For example, a normal intrusive thought might be misinterpreted by an individual with schizophrenia as an outside force trying to insert thoughts into their mind. The beliefs, and subsequent distress, is maintained by selective attention, previous experiences (Raune et al., 2009), and safety behaviours such as avoiding going out, shouting at voices or drinking alcohol (Northard, Morrison & Wells, 2008). Based on this model common components of CBT for psychosis include establishing a therapeutic alliance and collaborative formulation (Sivec & Montesano, 2012), psycho-education (Dudley et al., 2007), coping skill development (Tarrier, 2008), cognitive strategies to address delusions and hallucinations (Fowler et al., 1995), behavioural strategies to address both positive and negative symptoms (Sivec & Montesano, 2012), targeting comorbid affective states (Morrison et al., 2004) and relapse prevention (Morrison et al., 2004). These components are detailed in Appendix B.

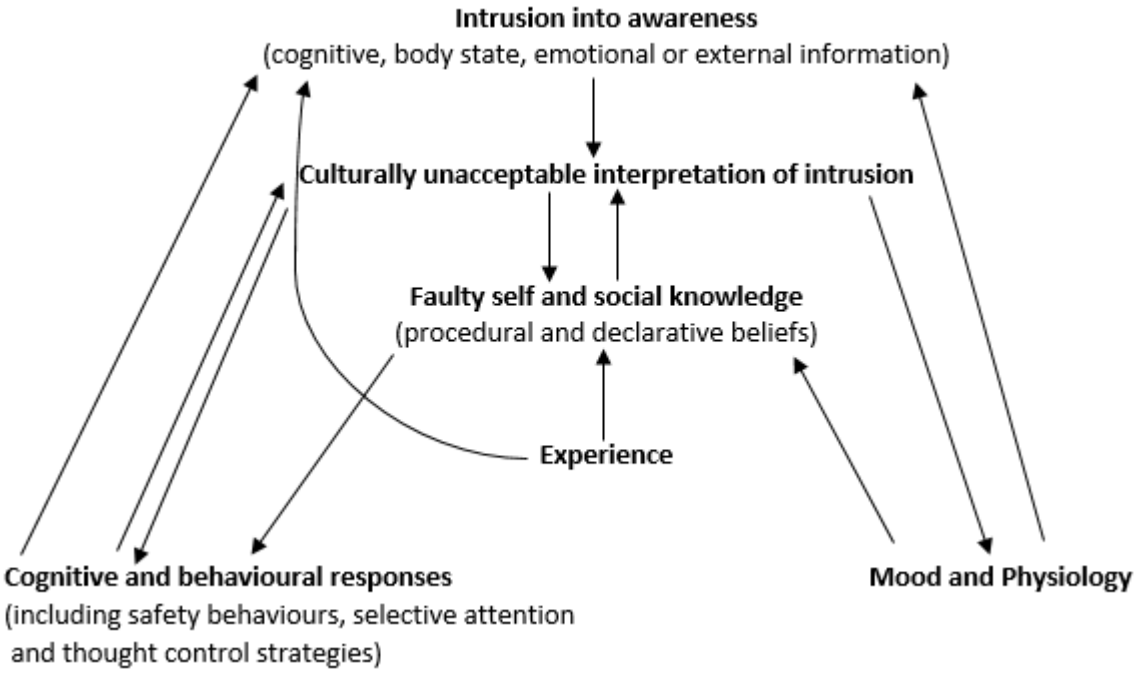

Figure 1. Morrison's (2001) model of psychosis.

Effectiveness of CBT for schizophrenia. There are now a number of clinical studies that have explored the efficacy of CBT and other psychological therapies in the treatment of schizophrenia. As a result, several meta-analyses that pool these results have now been conducted. An overview of results from these meta-analyses are indicated in Table 3 and demonstrate that effect sizes for CBT range from 0.04 to 1.25 (Newton Howes & Wood, 2013; Pilling et al., 2002), demonstrating significant variability. All report that cognitive behavioural therapy (CBT) is beneficial (Kurtz & Richardson, 2012; Pfmmatter, Junghan & Brenner, 2006; Zimmermann et al., 2005; Pilling et al., 2002; Wykes et al., 2008), though some have found that it is not significantly more beneficial than other psychosocial therapies (Jones et al., 2012). Other studies differed from each other in what symptoms or outcomes were treated

successfully with CBT, some finding successful improvements in outcomes for positive symptoms (Zimmermann et al., 2005; Pfmmatter et al., 2006), and others finding no results for positive symptoms, but beneficial effects for social cognition symptoms such as theory of mind and facial affect recognition (Kurtz & Richardson, 2012).

Table 3

Overview of current meta-analyses comparing CBT for Schizophrenia with control on measure of positive symptoms, negative symptoms, global symptoms and total symptoms

Author	*k*	N	Control Group Interventions	Effect Size			
				P	N	GP	T
Pilling et al. (2002)	8	393	SC	na	na	1.25	na
Zimmermann et al. (2005)	14	1484	WL, TAU, problem solving, recreation and SPT	0.37	na	na	na
Pfmmatter et al. (2006)	17	-	PE, ST	0.47	na	0.45	na
Wykes et al. (2007)	34	-	TAU	0.37	0.44	na	na
Kurtz &	19	692	Varied TAU, skills training	0.15	0.26	0.68	na

Richardson (2012)			groups				
Reckor & Beck (2012)	7	383	RC, problem solving, ST, BF, informal support	na	na	na	0.91
Jones et al. (2012)	20	-	ST, PE, Family Therapy	0.67	0.25	na	na
Newton-Howes & Wood (2013)	9	602	SC	na	na	na	0.04
Burns et al. (2014)	16	639	BF, PE, TAU, ST, WL, ST, SC	0.47	na	0.52	na
Jauhar et al. (2014)	50	-	TAU, WL	0.25	0.13	na	0.33
Velthorst et al. (2015)	35	2312	TAU, BF, PE, SC, WL, ST	na	0.09	na	na

Note. *k*=number of studies, N= number of participants, RC = Routine Care, ST supportive psychotherapy, BF befriending, SC standard care, WL wait list, TAU treatment as usual, SPT supportive psychotherapy. PE psychoeducation. CBT cognitive behavioural therapy. P= positive symptom measure, N= negative symptom measure, GP= general psychopathology measure, T= total symptoms measure; na= not assessed.

Limitations of current literature

Despite the numerous meta-analyses conducted to date there continues to be considerable variability in findings. This variability may be in part explained by the methodological short comings of previous meta-analyses in this field. One major problem with the literature in this field is that many important potential moderators of outcome have not previously been explored. One particularly important moderator of outcome may be study quality. Controlling for study quality is important in order to limit the reporting of biased treatment effects. To date, only two meta-analyses in the field have controlled for the quality of studies (Wykes et al., 2008; Velthorst et al., 2015). Velthorst found that higher study quality (typically found in more recent years) resulted in lower effect size (Velthorst et al., 2015). Similarly, Wykes et al. (2008) found studies with lower quality scores produced larger effect sizes, though they were cognizant that other factors also affected the trial results (Wykes et al., 2008).

Secondly, the comprehensiveness of quality of the CBT intervention may also account for inconsistent findings. For example CONSORT guidelines (Shulz, Altman & Moher, 2010) state that there needs to be "precise details of the interventions intended for each group and how and when they were actually administered" as well as a "description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants". To date no meta-analyses have examined the components of the CBT interventions that were delivered and have not used this as a moderator in meta-analytic studies. Therefore it is possible that studies that utilized or reported few components of an effective CBT treatment for schizophrenia would result in lower effect sizes than those who contained a more comprehensive

package. No studies to date have done this, and determining quality of interventions is difficult (Herbert & Bø, 2005), but it has been argued that the way the intervention has been delivered is a potential source of clinical heterogeneity (Herbert & Bø, 2005).

Thirdly, there are currently no meta-analyses that have examined the difference between manualised and non-manualised CBT treatments. This is problematic because manualised treatments have been found to out-perform non-manualised treatments in other psychological conditions including phobia and anxiety disorders in adults (Schulte et al., 1994; Stewart & Shambless, 2009; Sharpless & Barber, 2009; Wilson, 1996). Therefore this may also be an important factor in the schizophrenia research.

Fourthly, only one meta-analysis to date has looked at the stage of psychosis and its impact of the effectiveness of CBT. Zimmerman et al. (2005) found that CBT was more effective for patients in the acute or early phase of treatment than those with chronic psychosis (Zimmerman et al., 2005). However this meta-analysis is now quite outdated, performed over 10 years ago. More recent meta-analyses either use studies that do not examine these effects, or lump all studies in together, which may account for the variance in heterogeneity between studies.

Additionally, many studies differ in the type of control used, with some using some sort of passive control, such as a wait list control or treatment as usual conditions (Dunn et al., 2012; Durham et al., 2003), whilst others used an active control, such as supportive counselling (Pinto et al., 2009) or psycho-education (Cather et al., 2005). To date, one meta-analysis has found that studies using ‘active’ controls resulted in larger effect sizes than studies using ‘passive’ controls (Kurtz & Richardson, 2012). However, again most meta-analyses in this field group all control

groups together introducing unnecessary 'noise' to the data.

Finally, treatment format, in terms of whether the treatment is delivered in an individual or group setting may also account for differences in outcomes across meta-analyses. Two meta-analyses investigated treatment format and how it impacts on the outcome of CBT on schizophrenia (Wykes et al., 2008; Velthorst et al., 2015). These studies reported inconsistent findings, with Velthorst et al. (2015) finding that individual treatment resulted in higher effect sizes for reducing negative symptoms (Velthorst et al., 2015) and Wykes finding no evidence of a difference between the different treatment formats on symptom reduction (Wykes et al., 2008).

Given the inconsistent results and limitations of the existing meta-analyses, it is difficult to ascertain the efficacy of CBT for schizophrenia and therefore it is not known what is clinically the most effective intervention for a clinical psychologist to provide with this population. The aim of this meta-analysis is to address the abovementioned limitations by conducting a meta-analysis that a) considers the quality of the included studies; b) considers the components that constitute the CBT intervention used and measure how comprehensive the CBT intervention is; c) investigates the differences between manualised and non-manualised treatments; d) clearly defines the control group in terms of active or passive; e) investigates differences of CBT on acute and chronic presentations of schizophrenia; and f) considers the format of treatment to determine if individual or group formats result in larger effect sizes.

Method

Search strategy

Journal articles were identified through searches of PsychINFO, Scopus, Embase and Medline databases and were searched from 1990 to June 2014. The search terms ‘schizophrenia’, or ‘psychosis’ were combined with ‘cognitive behav* therapy’, ‘treatment’ and ‘trial’. Studies that were not in English language were excluded at the search level. Relevant studies were also identified through references of originally identified articles and published reviews, including meta–analyses. Study flow is included in Figure 2.

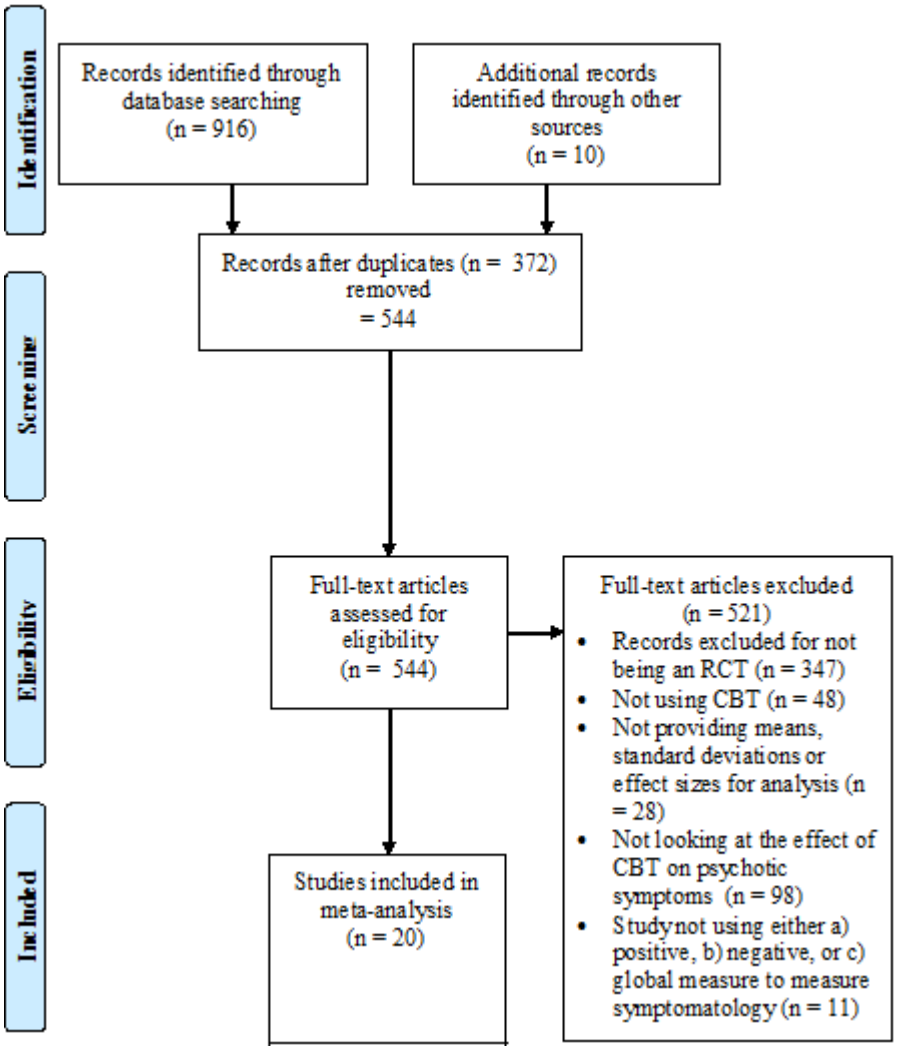

Figure 2. Study Flow**.** CBT= cognitive behavioural therapy. RCT= randomized controlled trial.

Inclusion criteria

Studies were included if 1) they were randomised control trials (RCTs); 2) they compared the effect of some variant of CBT to a non-CBT psychotherapy/control; 3) they provided sufficient information on outcome measures to calculate effect sizes; 4) they were investigating the effect of CBT on psychotic symptoms; 5) they used a measure of either positive symptoms, negative symptoms

or global psychopathology; 6) they were conducted after 1990; and 7) the study included original data (i.e., not duplicate data).

Data Collection and Synthesis

Intention-to-treat (ITT) data were used where possible, however completer data was used when this was not possible (indicated in Table 4). Data was analysed using Comprehensive Meta-Analysis Version 2.2 (Comprehensive Meta-Analysis, 2014). Pooled effect sizes with 95% confidence intervals (CI) (Hedges *g*) were calculated using a random effects model weighted for sample size and were calculated for total symptoms (i.e., the BPRS), positive symptoms (i.e., the PANSS positive scale or SAPS), negative symptoms (i.e., the PANSS negative scale or SANS), and general psychopathology symptoms (i.e., the PANSS general psychopathology (gp) scale). Consistent with previous interpretations, an effect size of 0.2 is considered a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen, 1988). Between-group effect sizes were calculated for each study according to the following formula: $\frac{X_1 - X_2}{SD_{pooled}}$, where X_1 represents the post-treatment score for the CBT condition and X_2 is the post-treatment score for the control group. The pooled standard deviation was derived using the formula $\frac{\sqrt{(N_1 - 1) \times {SD_1}^2 + (N_2 - 1) \times {SD_2}^2}}{N_1 + N_2 - 2}$. In this formula N_1 represents the CBT group sample, and N_2 the sample size for the control group. Likewise, SD_1 and SD_2 represent the standard deviations of the CBT group and control groups respectively. Cohen's *d* was then converted to Hedge's *g* by multiplying it with the correction *J* formula: $J(df) = 1 - \frac{3}{4_{df} - 1}$ (Borenstein et al., 2011).

Publication bias was examined using Begg and Maumdar's rank correlation (Begg & Mazumdar, 1994), Egger's test of the intercept (Egger et al., 1997), and

Duval & Tweedie's trim and fill method (Duval & Tweedie, 2000)**.** Heterogeneity was assessed using the Q test and I^2 statistics. An I^2 result of 25% is traditionally considered low, 50% moderate and 75% high levels of heterogeneity (Borenstein et al., 2009; Higgins et al, 2003).

Study moderators include 1) study quality; 2) CBT comprehensiveness; 3) manualised vs. non-manualised interventions; 4) stage of psychosis; 5) active vs. passive control, and 6) treatment format (individual vs. group). Study quality was assessed with the Clinical Trials Assessment Measure (CTAM; Tarrier & Wykes, 2004), which provides a study quality metric out of 100 taking into consideration 6 domains of the trial: sample size, recruitment, treatment allocation, assessment of outcome, control group, description of treatment and analysis. Higher scores on the CTAM indicate a higher quality study. The comprehensiveness of the CBT intervention was assessed with the CBT for psychosis comphrensiveness scale (CPCS), which was developed specifically for this study and contains a checklist of 20 CBT components that are often included in treatments for schizophrenia (see Appendix C). Categorical variables were assessed by a Q-test based on analysis of variance (Borenstein et al., 2009) and continuous variables were assessed by univariate meta-regression analysis (Borenstein et al., 2009).

Results

Description of Studies

The initial search identified 926 articles. A flowchart of the screening process is shown in Figure 1.Three hundred and seventy two duplicates were removed, resulting in 544 studies. These were then screened based on the inclusion criteria, first by reading the abstract and then the full article if it was not clear if the inclusion/exclusion criteria were met. Five-hundred and twenty-four articles were excluded for not meeting inclusion/exclusion criteria, resulting in 23 studies with a total of 2,639 participants. The majority of studies (60%) were conducted in the UK and the total duration of CBT ranged from 4 months to 18 months. Information on the included studies is outlined in Table 4.

Table 4.

Characteristics of the studies included in meta-analysis

Study	Country	N	Control group	Treatment stage	Outcome measure	CBTCS	Use of treatment manual	Format	CTAM
Barrowclough et al. (2006)	UK	113	P	Chronic	PANSS	12	Y	G	74
Barrowclough et al. (2010)	UK	327	A	NS	PANSS	13	Y	I	87
Bechdolf et al. (2005)	Germany	88	A	Early	PANSS	12	N	G	85
Cather et al. (2005)	US	30	A	NS	PANSS	9	N	I	71
Dunn et al. (2012)	UK	273	P	Early	PANSS	10	Y	I	88
Durham et al. (2003)	UK	43	P	Chronic	PANSS	10	N	I	72

					PSYRATS				
Granholm et al. (2013)	US	79	A	NS	PANSS, SANS	11	Y	G	72
Granholm et al. (2014)	US	149	A	NS	PANSS, SANS	10	Y	G	81
Gumley et al. (2003)	UK	144	A	NS	PANSS	10	N	I	69
Haddock et al. (1999)	UK	20	A	Early	BPRS	12	Y	I	58
Haddock et al. (2009)	UK	71	P	NS	PANSS	16	Y	I	65
Jackson et al. (2007)	AUS	62	P	Early	BPRS, SANS	11	Y	I	81
Kuipers et al. (1997)	UK	60	A	Chronic	BPRS	12	Y	I	68
Kuipers et al. (2004)	UK	59	P	Early	PANSS	6	N	I	54

Lewis et al. (2002)	UK	315	P	Early	PANSS	11	Y	I	74
Li et al. (2014)	China	192	A	NS	PANSS	15	Y	I	75
Lincoln et al. (2012)	Germany	80	P	NS	PANSS	15	Y	I	82
Peters et al. (2010)	UK	74	P	NS	PANSS	9	N	I	68
Pinto et al. (1999)	Italy	41	A	NS	BPRS, SAPS, SANS	10	N	I	27
Rector et al. (2012)	Canada	42	P	NS	PANSS	15	N	I	67
Tarrier et al. (2004)	UK	315	P	Early	PANSS	13	Y	I	90
Valmaggia et al. (2005)	Netherlands and Belgium	62	A	NS	PANSS	9	Y	I	78

Note. CBTCS= CBT component score. US= United States UK= United Kingdom. AUS= Australia. A= Active Control. P= Passive Control. NS= Not Stated. PANSS positive and negative syndrome scale, BPRS brief psychiatric rating scale, SAPS Scale for the Assessment of Positive Symptoms, SANS scale for the assessment of negative symptoms, CPRS comprehensive psychiatric rating scale, PSYRATS psychotic symptom rating scales, SCS schizophrenia change scale, BRIANS brief assessment of negative symptoms scale. Y= Yes. N= No. G= Group intervention. I= Individual Intervention.

Data Synthesis

Total Symptoms. Between-group effect sizes on measures of total symptoms are available for 11/22 (50%) studies. As indicated in Table 5 there was a small (g = 0.19) and non-significant between-group effect size between CBT and control conditions. These studies were found to be moderately heterogeneous (Q_1=27.55, p=.00; I^2=63.70). The forest plot (Figure 3) demonstrates that the majority of studies demonstrate a mean positive effect for CBT, though all studies cross the 0.00 effect line, showing they do not differ significantly from no effect.

The pre-treatment to post-treatment effect size was not moderated by quality of treatment (Q_1=1.18, p=.27; low quality: g=0.53; 95% CI: -0.23-1.31; high quality: g=-0.01; 95% CI: -0.01-0.00), comprehensiveness of the CBT treatment (Q_1=0.70, p=.40; low comprehensiveness: g=-0.05; 95% CI: -0.15-0.07; high comprehensiveness: g=0.65; 95% CI: -0.61-1.92), or treatment manualisation (Q_1=0.00, p=.99; manualised: g=0.19; 95% CI: -0.05-0.43; non-manualised: g=-0.19; 95% CI: -0.82-1.20). Additionally, the treatment effect size was also not moderated by stage of illness (Q_1=0.22, p=.97; acute: g=0.17; 95% CI: -0.05-0.39; chronic: g=0.13; 95% CI: -0.24-0.49), the type of control group used (Q_1=0.01, p=.90; active: g=0.11; 95% CI: -1.16-1.37; passive: g=0.19; 95% CI: -0.04-0.42), or the treatment format used (Q_1=0.07, p=.79; group: g=0.25; 95% CI: -0.14-0.65; individual: g=0.19; 95% CI: -0.06-0.44).

Positive Symptoms. Between-group effect sizes on measures of positive symptoms are available for 20/22 (91%) studies. As indicated in Table 5 there was a small (g = 0.16) but significant between-group effect size between CBT and control conditions. These studies were found to be moderately heterogeneous (Q_1=33.89,

p=.03; I^2=38.04). The forest plot (Figure 4) indicates a more positive result for CBT on positive symptoms and less variability than total symptoms.

The pre-treatment to post-treatment effect size was not moderated by quality of treatment (Q_1=2.28, *p*=.13; low quality: *g*=0.62; 95% CI: -0.00-1.25; high quality: *g*=-0.00; 95% CI: -0.01-0.00), comprehensiveness (Q_1=0.21, *p*=.65; low comprehensiveness: *g*=-0.01; 95% CI: -0.05-0.03; high comprehensiveness: *g*=0.26; 95% CI: -0.22-0.74), or treatment manualisation (Q_1=0.11, *p*=.74; manualised: *g*=0.16; 95% CI: 0.05-0.27; non-manualised: *g*=-0.11; 95% CI: -0.16-0.38). Additionally, the treatment effect size was also not moderated by stage of illness (Q_1=6.02, *p*=.11; acute: *g*=-0.14; 95% CI: -0.55-0.27; chronic: *g*=0.02; 95% CI: -0.31-0.35), the type of control group used (Q_1=0.27, *p*=.60; active: *g*=0.08; 95% CI: -0.16-0.32; passive: *g*=0.15; 95% CI: 0.04-0.27), or the type of treatment format used (Q_1=1.39, *p*=.24; group: *g*=-0.04; 95% CI: -0.43-0.34; individual: *g*=0.20; 95% CI: 0.10-0.29).

Negative Symptoms. Between-group effect sizes on measures of negative symptoms are available for 20/22 (91%) studies. As indicated in Table 5 there was a small (*g* = 0.12) and non-significant between-group effect size between CBT and control conditions. These studies were found to be moderately heterogeneous (Q_1=31.48, *p*=.03; I^2=39.66). The forest plot (Figure 5) indicates large variability between studies, with a small overall positive result for CBT on negative symptoms.

The pre-treatment to post-treatment effect size was moderated by quality of treatment (Q_1=5.73, *p*=.01), with low quality studies (*g*=0.86; 95% CI: 0.24-1.49) resulting in higher effect sizes than high quality studies (*g*=-0.01; 95% CI: -0.02—0.00). The pre-post treatment effect size was not moderated by comprehensiveness (Q_1=1.19, *p*=.27; low comprehensiveness: *g*=0.02; 95% CI: -0.02-0.06; high

comprehensiveness: *g*=-0.17; 95% CI: -0.67-0.33) or treatment manualisation (Q_1=0.10, *p*=.75; manualised: *g*=0.10; 95% CI: -0.07-0.27; non-manualised: *g*=-0.14; 95% CI: -0.06-0.35). Additionally, the treatment effect size was also not moderated by stage of illness (Q_1=1.72, *p*=.63; acute: *g*=-0.03; 95% CI: -0.43-0.38; chronic: *g*=0.06; 95% CI: -0.33-0.45), or the type of control group used (Q_1=1.32, *p*=.24; active: *g*=0.05; 95% CI: -0.09-0.19; passive: *g*=0.21; 95% CI: -0.03-0.21). Finally, treatment effect size was moderated by format of treatment (Q_1=5.29, *p*=.02), with individual treatment (*g*=0.19; 95% CI: 0.04-1.34) outperforming group treatments (*g*=-0.10; 95% CI: -0.29-0.10).

Measures of Global Symptomatology. Finally, between-group effect sizes on measures of global symptoms are available for 18/22 (82%) studies. As indicated in Table 5 there was a small (*g* = 0.12) and non-significant between-group effect size between CBT and control conditions. These studies were found to be moderately heterogeneous (Q_1=69.09, *p*=.00; I^2=75.40). The forest plot (Figure 6) shows more studies with larger positive effect sizes, however due to the high degree of variability between studies, the overall effect is still small.

The pre-treatment to post-treatment effect size was moderated by quality of treatment (Q_1=8.22, *p*=.00), with low quality studies (*g*=0.97; 95% CI: 0.35-1.60) resulting in higher effect sizes than high quality studies (*g*=-0.01; 95% CI: -0.02—0.00). The pre-post treatment effect size was not moderated by comprehensiveness (Q_1=1.20, *p*=.27; low comprehensiveness: *g*=0.02; 95% CI: -0.02-0.07; high comprehensiveness: *g*=-0.23; 95% CI: -0.77-0.32) or treatment manualisation (Q_1=0.23, *p*=.63; manualised: *g*=0.17; 95% CI: -0.05-0.39; non-manualised: *g*=-0.04; 95% CI: -0.41-0.50). Treatment effect size was moderated by stage of illness (Q_1=9.45, *p*=.02), chronic presentations (*g*=0.38; 95% CI: 0.06-0.71) showing higher

effect sizes than acute stages of illness (*g*=-0.69; 95% CI: -1.29—0.08) indicating that CBT may be more effective on global psychopathology symptoms of schizophrenia in chronic stages of the illness. However due to the small number of studies in this comparison these results should be interpreted with caution. Treatment effect size was also moderated by control group used (Q_1=3.69, *p*=.05), with passive controls (*g*=0.28; 95% CI: 0.04-0.53) showing higher effect sizes than active controls (*g*=-0.15; 95% CI: -0.53-0.22). Finally, the treatment effect size was not moderated by the type of treatment format used (Q_1=1.63, *p*=.20; group: *g*=-0.32; 95% CI: -1.12-0.47; individual: *g*=0.21; 95% CI: 0.01-0.41).

Table 5

Post-treatment group contrast analysis details

Measure	Studies *k*	Effect size (*g*) (95% CI)	*p* Value	Q Statistic	p Value	I^2
Total	11	0.19 (-0.04-0.42)	.09	27.55	0.00	63.69
Positive	22	0.16 (0.05-0.28)	.01	33.89	0.04	38.04
Negative	20	0.12 (-0.01-0.24)	.07	31.48	0.04	39.66
Global	18	0.12 (-0.09-0.33)	.26	69.09	0.00	75.40

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Tarrier et al 2004a	1.157	0.305	0.093	0.559	1.754	3.793	0.000
Tarrier et al 2004b	0.103	0.276	0.076	-0.438	0.644	0.372	0.710
Tarrier et al 2004c	0.335	0.296	0.087	-0.245	0.914	1.132	0.258
Lewis et al 2002	0.144	0.140	0.020	-0.130	0.419	1.031	0.303
Pinto et al 1999	0.718	0.332	0.111	0.067	1.370	2.161	0.031
Haddock et al 1999	-0.572	0.440	0.194	-1.435	0.290	-1.301	0.193
Kuipers et al 1997	0.342	0.289	0.084	-0.225	0.908	1.183	0.237
Barrowclough et al 2010	-0.185	0.121	0.015	-0.422	0.051	-1.536	0.125
Dunn et al 2012	0.213	0.189	0.036	-0.158	0.583	1.125	0.260
Durham et al 2003	-0.312	0.301	0.091	-0.903	0.278	-1.036	0.300
Barrowclough et al 2006	0.252	0.201	0.040	-0.142	0.646	1.252	0.211
	0.117	0.064	0.004	-0.008	0.242	1.830	0.067

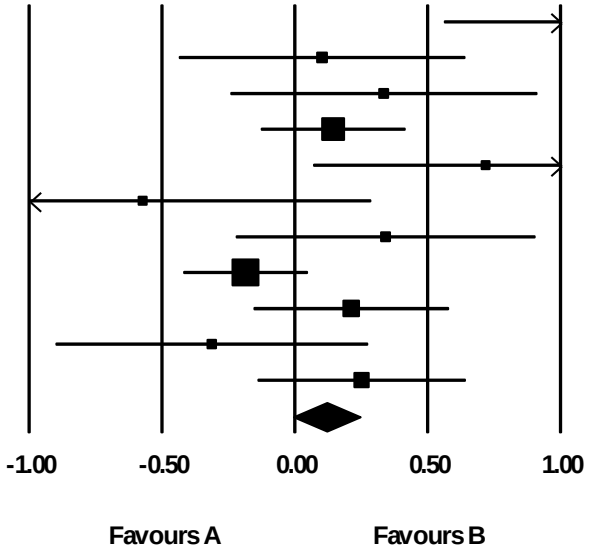

Figure 3. Forest plot of studies in the meta-analysis of total symptoms.

Studyname	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lincoln et al 2012	0.411	0.224	0.050	-0.028	0.849	1.834	0.067
Gumley et al 2003	0.347	0.167	0.028	0.020	0.675	2.079	0.038
Li et al 2014	0.040	0.144	0.021	-0.241	0.322	0.281	0.779
Jackson et al 2008	0.049	0.271	0.074	-0.483	0.580	0.180	0.857
Bechdolf et al 2005	-0.796	0.231	0.053	-1.249	-0.344	-3.450	0.001
Cather et al 2005	0.046	0.368	0.135	-0.675	0.767	0.126	0.900
Valmaggia et al 2005	0.305	0.266	0.071	-0.217	0.827	1.144	0.252
Bechdolf et al 2004	0.023	0.212	0.045	-0.393	0.439	0.107	0.915
Lewis et al 2002	0.123	0.140	0.020	-0.152	0.397	0.876	0.381
Pinto et al 1999	0.615	0.330	0.109	-0.031	1.261	1.865	0.062
Barrowclough et al 2010	-0.006	0.120	0.015	-0.242	0.230	-0.049	0.961
Granholm et al 2013	0.107	0.261	0.068	-0.404	0.618	0.411	0.681
Granholm et al 2014	0.406	0.224	0.050	-0.032	0.845	1.817	0.069
Haddock et al 2009	0.164	0.186	0.035	-0.202	0.529	0.878	0.380
Kuipers et al 2004	0.161	0.274	0.075	-0.376	0.698	0.588	0.556
Rector et al 2003	0.341	0.218	0.047	-0.086	0.768	1.566	0.117
Peters et al 2010	0.336	0.269	0.072	-0.191	0.863	1.248	0.212
Durham et al 2003	-0.016	0.307	0.094	-0.618	0.586	-0.052	0.958
Barrowclough et al 2006	0.034	0.200	0.040	-0.359	0.426	0.168	0.866
	0.118	0.047	0.002	0.027	0.210	2.528	0.011

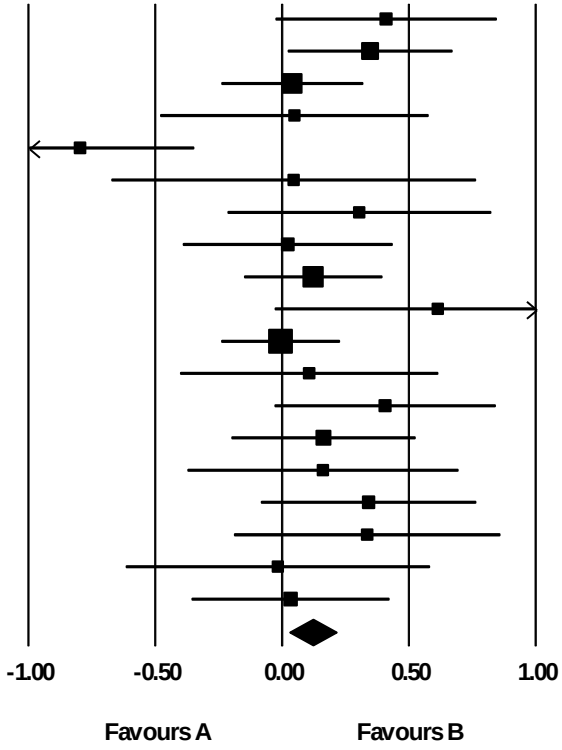

Figure 4. Forest plot of studies in the meta-analysis of positive symptoms.

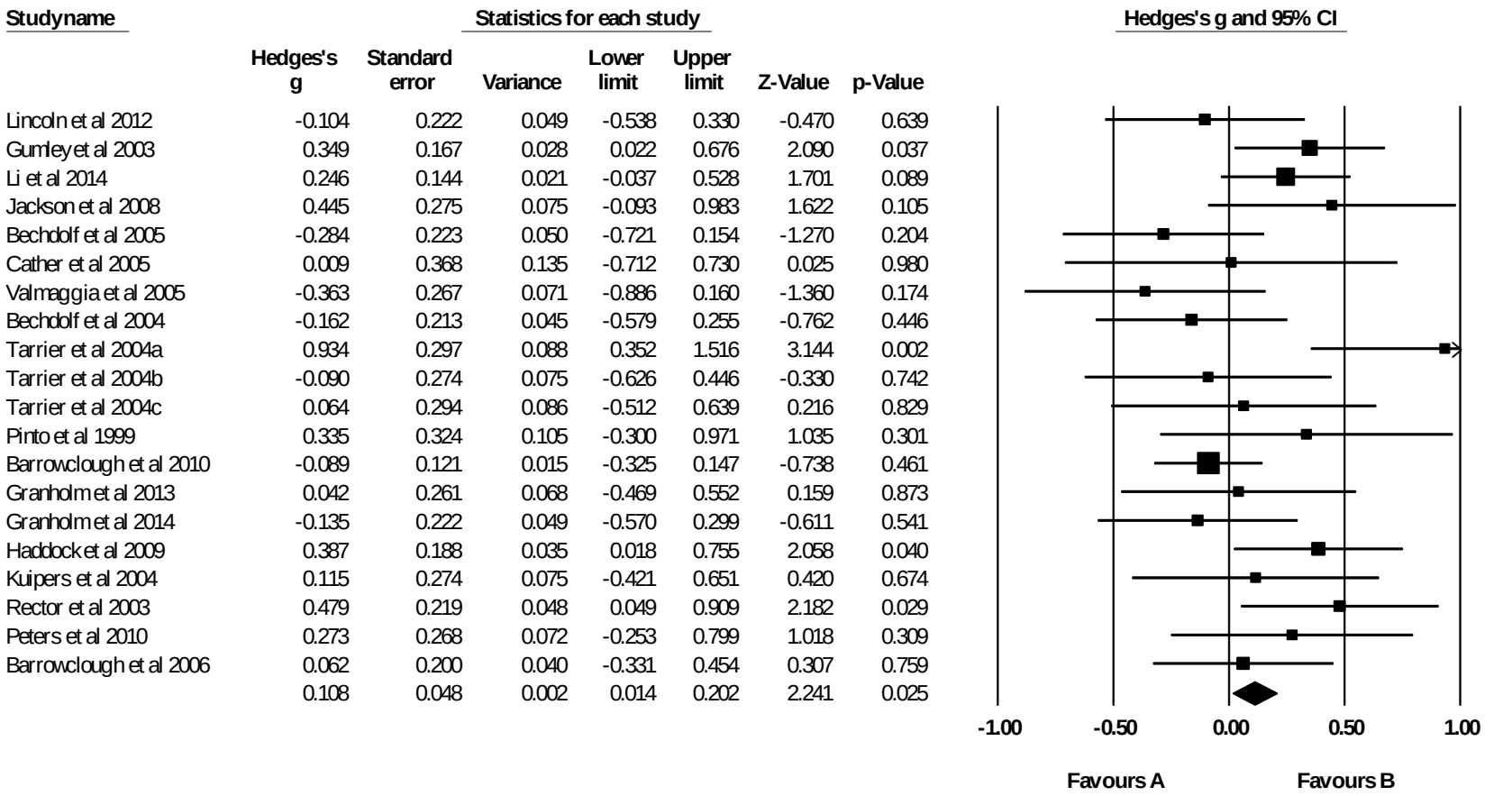

Figure 5. Forest plot of studies in the meta-analysis of negative symptoms.

Studyname	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Lincoln et al 2012	0.391	0.224	0.050	-0.047	0.829	1.750	0.080
Gumley et al 2003	0.294	0.167	0.028	-0.033	0.620	1.762	0.078
Li et al 2014	0.108	0.144	0.021	-0.174	0.390	0.752	0.452
Bechdolf et al 2005	-1.005	0.236	0.056	-1.467	-0.542	-4.259	0.000
Valmaggia et al 2005	-0.130	0.265	0.070	-0.649	0.390	-0.490	0.624
Bechdolf et al 2004	-0.386	0.214	0.046	-0.806	0.034	-1.801	0.072
Tarrier et al 2004a	1.010	0.300	0.090	0.423	1.597	3.371	0.001
Tarrier et al 2004b	0.072	0.273	0.075	-0.464	0.608	0.262	0.794
Tarrier et al 2004c	0.375	0.296	0.088	-0.205	0.956	1.266	0.205
Pinto et al 1999	0.718	0.332	0.111	0.067	1.370	2.161	0.031
Haddock et al 1999	-0.572	0.440	0.194	-1.435	0.290	-1.301	0.193
Kuipers et al 1997	0.342	0.289	0.084	-0.225	0.908	1.183	0.237
Barrowclough et al 2010	-0.291	0.121	0.015	-0.528	-0.053	-2.401	0.016
Haddock et al 2009	0.145	0.186	0.035	-0.221	0.510	0.776	0.438
Kuipers et al 2004	-0.305	0.275	0.076	-0.844	0.234	-1.108	0.268
Rector et al 2003	0.616	0.221	0.049	0.182	1.050	2.784	0.005
Peters et al 2010	0.446	0.270	0.073	-0.084	0.975	1.648	0.099
Barrowclough et al 2006	0.401	0.202	0.041	0.004	0.797	1.981	0.048
	0.072	0.051	0.003	-0.027	0.172	1.430	0.153

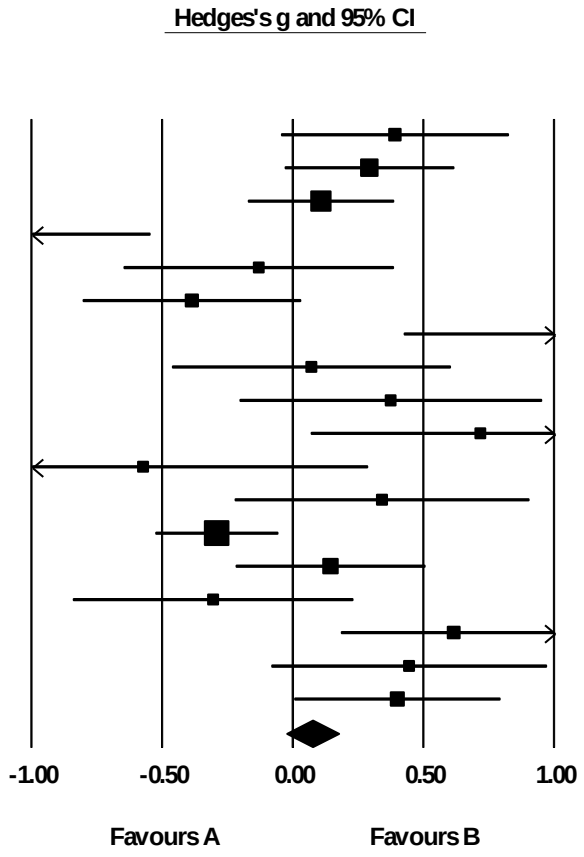

Figure 6. Forest plot of studies in the meta-analysis of global psychopathology.

Publication Bias. Funnel plots of the studies in the four main analyses are shown in Figure 7 (total symptoms), Figure 8 (positive symptoms), Figure 9 (negative symptoms), and Figure 10 (global psychopathology); and results of the analyses are shown in Table 6. Begg and Mazundar's test and Egger's test was not significant for any of the four main analyses. The trim and fill method imputed 2 studies in the meta-analysis of total symptoms, reducing the effect size from 0.19 to 0.05. For the meta-analysis of positive symptoms, the trim and fill imputed eight studies, reducing the effect size from 0.13 to -0.13. No studies were imputed for negative symptoms, suggesting no missing studies. Two studies were imputed for meta-analysis of global psychopathology, adjusting the effect size from 0.12 to -0.17.

Table 6

Results of tests for publication bias in the analyses of total symptoms, positive symptoms, negative symptoms and global psychopathology

		Effect size (95% CI)		Begg & Mazumdar's test		Egger's test	
	k	Unadjusted	Trim and Fill adjusted	*t*	*p*	*t*	*p*
Total	11	0.19 (-0.04-0.42)	0.05 (-0.20-0.31)	0.25	0.27	1.26	0.23
Positive	22	0.12 (0.01-0.24)	-0.01 (-0.13-0.10)	0.11	0.48	0.67	0.50
Negative	20	0.11 (-0.01-0.24)	0.11 (-0.01-0.24)	0.08	0.58	0.49	0.67
Global	18	0.12 (-0.08-0.33)	0.04 (-0.17-0.25)	0.13	0.45	0.97	0.35

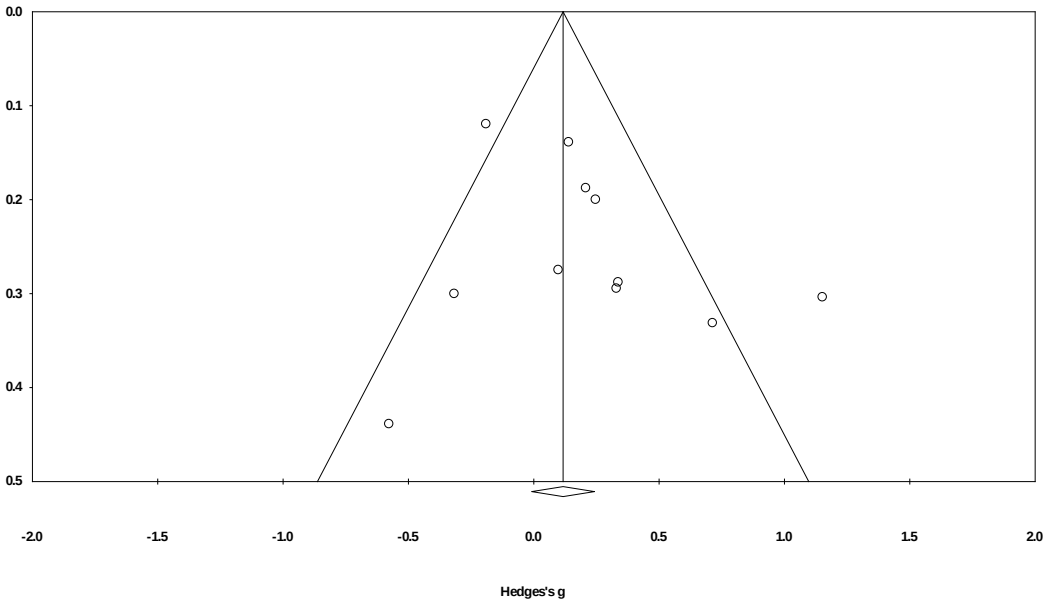

Figure 7. Funnel plot of studies in the meta-analyses of total symptoms.

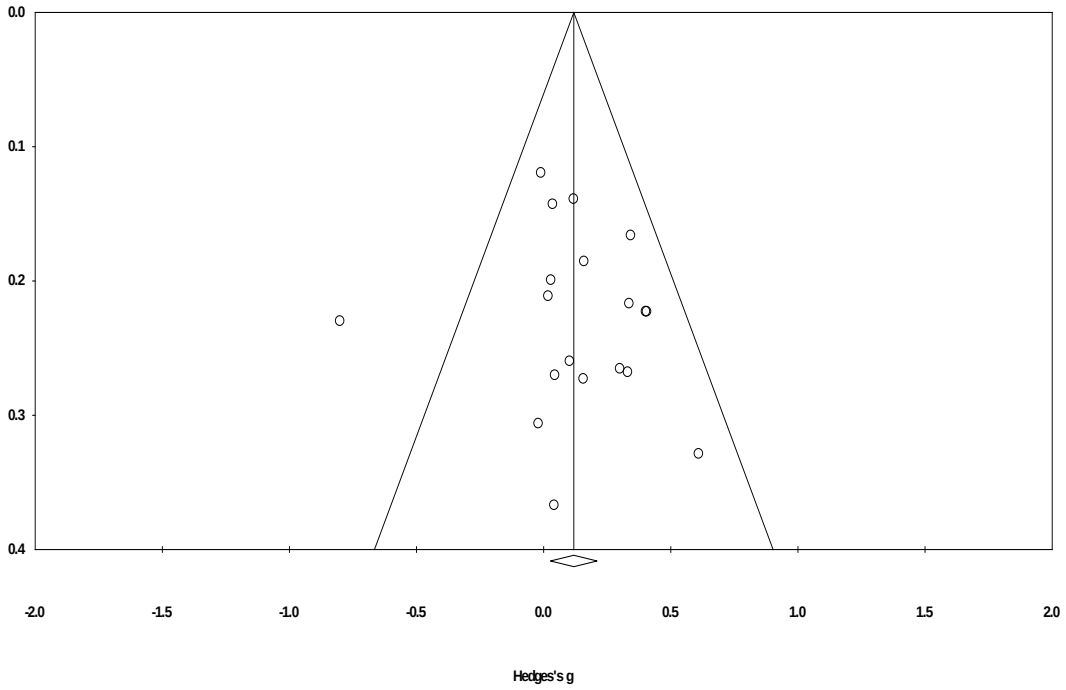

Figure 8. Funnel plot of studies in the meta-analyses of positive symptoms.

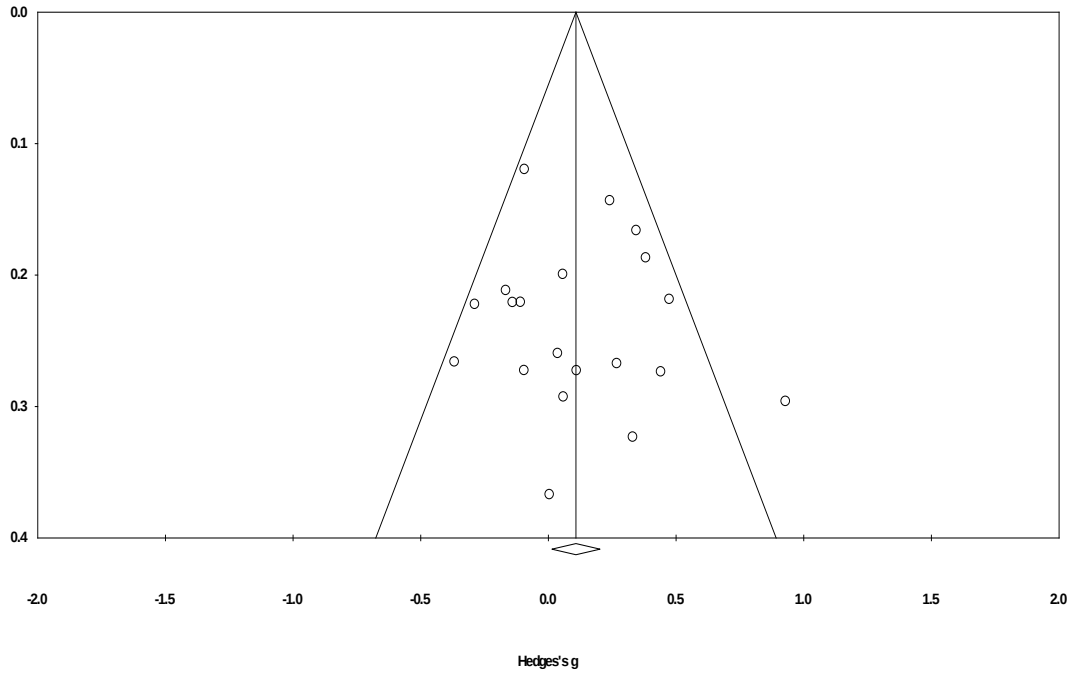

Figure 9. Funnel plot of studies in the meta-analyses of negative symptoms.

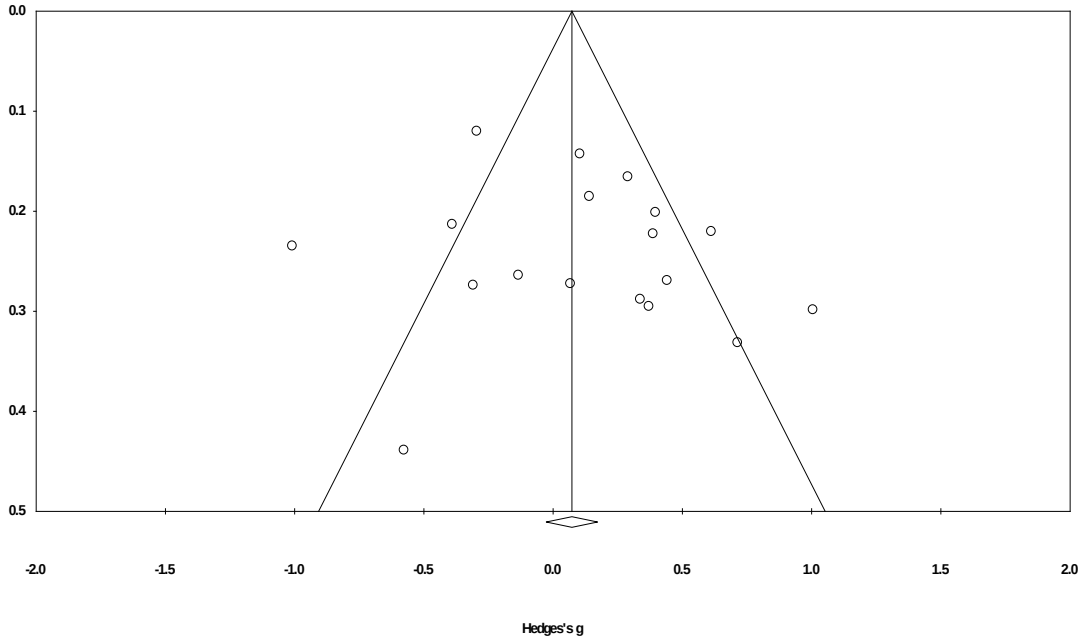

Figure 10. Funnel plot of studies in the meta-analyses of global psychopathology.

Discussion

Several meta-analyses have examined the effect of CBT on symptoms of schizophrenia. However the results of these studies are mixed and are also plagued with methodological limitations. Therefore, it remains difficult to determine if CBT is effective in reducing symptoms of schizophrenia. The aim of this study was to address the methodological limitations of existing meta-analyses and quantify the effectiveness of CBT for schizophrenia using a meta-analytic approach. Important moderators were also examined including 1) study quality; 2) comprehensiveness of treatment components; 3) manualised vs. non-manualised approaches; 4) stage of illness; 5) type of control group used; and 6) treatment format.

Twenty-two RCTs were identified that measured changes in total, positive, negative and global psychopathology symptoms in response to CBT. The results of this meta-analysis found effect sizes for all symptoms measured to be in the 'small' range, and only CBT for positive symptoms produced a significant result. This finding is consistent with some of the more recently conducted meta-analyses of other authors (e.g., Velthorst et al., 2015; Jauhar et al., 2014; Newton-Howes & Wood, 2013), who found CBT produced only small effect sizes in symptom reduction (0.04-0.33).

When looking at the effect of study quality on outcome it was found that for negative symptoms and global psychopathology symptoms, the higher quality trials produced lower effect sizes. This replicates in part the finding of Wykes et al., (2008) and Velthorst et al., (2015), who found for all symptom types significant differences in effect sizes of lower versus higher quality studies using the same measure (CTAM). Wykes (2008) found that high CTAM studies produced effect sizes of between 0.08 and 0.22. Wykes (2008) however used a cutoff score of 65 to

differentiate between high and low studies, rather than a continuous variable as used in this analysis, which may account for the difference. There was no effect of study quality on total and positive symptoms.

There is some discussion that the effects of CBT in clinical trials have declined linearly since their introduction (Johnsen & Friborg, 2015). In their meta-analysis of CBT for the treatment of depression, Johnsen and Friborg (2015) found that measures from self-report, clinician rating and rates of remission declined steadily, with modern trials providing less symptom reduction than the seminal studies that was not due to study design, number of participants, or study samples. It was suggested that these findings may be due to the higher quality of trials now being executed (Wykes et al., 2008), adherence levels to treatment manuals (Shafran et al., 2009), and the placebo effect (Johnsen & Friborg, 2015).

To understand whether the type of CBT interventions used impacted on its effectiveness, a checklist was developed in this study to measure how many of the common components important to CBT for psychosis were included in the identified studies. Analysis found that effect sizes were no different for studies that only reported using a few common components than studies that reported using most of the identified components. Velthorst et al. (2015) looked at whether the number of behavioural components used in treatment (low versus high) had an impact on effect size. They found that it did not explain the heterogeneity found between studies, but there was a trend effect indicating that a more behavioural approach was slightly more effective in treating negative symptoms than a cognitive approach (Velthorst et al., 2015). This stands to reason, as behavioural activation improves anhedonia and desire for social contact in depression, with large effect sizes (SMD= 0.74) found in a recent meta-analysis (Ekers et al., 2014).

There were also no differences between the effect sizes of studies that adhered to a manualised treatment program and those that used non-manualised treatment interventions. This is the first study to date that that investigated this moderator in a meta-analysis of the effect of CBT for schizophrenia. No studies to date have examined the difference between these two types of treatment approaches, though many use measures of treatment adherence, indicating the importance of treatment manuals and protocols to show evidence based practice and reliable results (Rollinson et al., 2007; Durham et al., 2003; Kuipers et al., 1997; Turkington & Kingdon, 2000). Some research has indicated that manualisation leads to less effective outcomes due to limiting therapist flexibility (Castonguay et al.,1996), though studies examining this have reported that using manualized treatments does not limit flexibility (Connolly Gibbins et al., 2003), and therefore manualized and non-manualised treatments should not demonstrate differences in effect.

The stage of illness (e.g., acute vs. chronic) was also investigated as a potential treatment moderator. Overall there was no effect of the stage of the illness on total symptoms, positive or negative symptoms, though global psychopathology symptoms were alleviated more in chronic conditions. Only one other meta-analysis has explored the difference between stages of illness on outcome of CBT using a meta-analytic approach. Zimmerman et al (2005) found a non-significant trend in favour of CBT for those in an acute phase of illness. Mean weight effect sizes for the acute phase were moderate (g=0.57) and small to moderate in chronic phases (g=0.27), though the two way ANCOVA was non-significant. These results are tenuous due to the methodological rigor and number of studies included in analyses. Further studies should be completed to examine the different symptom profiles in

each stage of the illness, mapping with effective treatment components as mentioned above to determine the most clinically effective treatment program for the individual.

There was little difference in effect sizes when comparing CBT to treatment as usual or another 'passive' control, and between CBT and a more active control, such as supportive therapy. This study did find that some of the heterogeneity between studies measuring global psychopathology symptoms may be attributed to control type, with studies employing a passive control (g = 0.28) resulting in a larger effect size than those using an active control (g=-0.15). This is a similar finding to that of Burns et al. (2014) and Sarin et al. (2011), who found that type of control group used did not result in significantly different effect sizes. This is in contrast however to the findings of Kurtz and Richardson (2012) however, who found studies with active control conditions resulted in larger effect sizes (d = 1.05) than those utilizing passive control conditions (d = -0.29).

Finally, it was found that individual treatment (g = 0.19) was superior to group intervention (g = -0.10) in the alleviation of negative symptoms of schizophrenia, but treatment format was not important for the alleviation of other symptom types (total, positive and general psychopathology). This result replicates the results of Velthorst et al. (2015) who found that individual treatments reduced negative symptoms significantly more than group treatments. This finding has also been found in other psychological conditions including social anxiety disorder (Hedman et al., 2013) and bulimia nervosa (Chen et al., 2003). Potentially, those who find social contact and connectedness difficult or uninteresting, such as those with schizophrenia will benefit from a more individualized and personalized approach.

Why isn't CBT effective for symptom reduction in schizophrenia?

Recent meta-analyses (e.g., Velthorst et al., 2015; Newton-Howes & Wood, 2013) have now consistently shown that CBT for schizophrenia results in small treatment effects. This is a significant contrast to the successful use of CBT for other psychiatric conditions including panic disorder, social anxiety disorder, and depression (Westen & Morrison, 2001; Acarturk et al., 2009; Hans & Hiller, 2013). However, few authors to date have discussed potential reasons why CBT produces small treatment effects. There may be a number of reasons for the small effect size of CBT for schizophrenia compared with other psychological conditions.

Firstly, one potential reason for this small effect size is that in contrast to conditions such as panic disorder, social anxiety disorder, and depression mentioned above, schizophrenia is characterized by low levels of insight (Amador & Kronengold, 2004) and it has been suggested that CBT may be more effective for those who hold less conviction about these delusions and beliefs (Brabban et al., 2009). Secondly, another consideration in the effectiveness of CBT for schizophrenia is the length of treatment. Clinical guidelines recommend a minimum of 16 sessions of CBT (NICE, 2014), which if delivered weekly would equate to 4 months of treatment. The length of treatment within the selected studies in this analysis varied from 5 weeks to 12 months, however even studies with longer treatments, such as 12 months, did not result in better results. For example, the Barrowclough et al. (2010) study delivered CBT over a 12 month period, but the result was that CBT was not significantly superior to control, and did not result in a large effect size (Barrowclough et al., 2012). Recently, there have been promising results found by investigating intensive approaches to CBT for other psychological conditions (Ehlers et al., 2014; Teng et al., 2015; Knuts, 2015; Foa et al., 2005) and

this may be of benefit to individuals with schizophrenia who require consistent and regular support to complete practice tasks or behavioural experiments, or for those that lack in social skills that could benefit from regular practice and skills training. Further, it may work well to engage individuals in intensive treatment during a stable phase of their illness, rather than risk putting treatment on hold, or gains being lost, during an acute phase.

Limitations

The aim of this study was to investigate the specific effect of CBT on symptom severity measures (i.e., total symptom scores, positive symptoms, negative symptoms and general psychopathology scores). This limited the number of studies that could be included in the meta-analysis as many studies including measures of constructs other than symptom severity such as relapse, hospitalization, self-esteem, or violence. The effect of CBT on these other important constructs was not assessed in this study and could be considered a limitation of the study. In addition, the number of studies included in some of the moderator analyses were very small, and therefore the power to detect true relationships may be reduced and thus these results should be interpreted with caution.

Further study/recommendations

Overall, it is clear that the recommendations outlined by Pilling et al. (2002) 10 years ago, which have been echoed more recently (Rector & Beck, 2012; Newton-Howes & Wood, 2013), are still relevant today, and that more studies examining which components of CBT work for which patient populations are needed. Firstly, it may be useful to look at dismantling studies in this field, which have not been conducted to date. Dismantling studies have been useful to determine which components of CBT are most effective for anxiety disorders for both children

and adults (Ale et al, 2015; Bryant et al., 2003) and depression (Dimidjian et al., 2006; Kennard et al., 2009).

Secondly, it may also be useful to investigate the supports surrounding the individual being treated and to use any possible social support networks to help the client understand concepts, practice tasks between sessions, and work towards their goals more holistically. Several studies have now started to look at how CBT can enhance other areas of functioning with promising results, such as CBT and vocational readiness (Lysaker et al., 2009) psychosocial rehabilitation programs (Pfmatter et al., 2006), or CBT on depression (Jones et al., 2012). This has been used successfully in other diagnostic groups including depression, bipolar disorder, substance use and anxiety (Minjoo et al., 2014; Zhong et al., 2015).

Thirdly, while this study did not find a difference in effectiveness for CBT across acute and more chronic phases of illness, other studies have found such differences for certain stages (Zimmerman, 2005), and others have found CBT may be of more benefit in key transitional periods, such as shifts from hospital or institutions such as prison to community (Thornicroft & Susser, 2001). An additional limitation of this field is that the treatment stage is not clearly described for all included participants. There are an increasing number of studies now looking at intervention in the prodromal or early stages of the illness with promising outcomes (Matsumoto et al., 2013; van der Gaag, 2012), and thus more studies investigating the effect of CBT in all phases is needed.

Fourthly, treatment modalities other than CBT also deserve investigation in the future as it is possible that CBT may not be the most effective treatment for this population. Currently, other therapies such as compliance therapy (Kemp et al., 1998; O'Donnell et al., 2003), acceptance and commitment therapy (Bach & Hayes,

2002; Gaudiano & Herbert, 2006), and metacognitive training (Moritz et al., 2010; Moritz et al., 2011), show promise in reducing symptoms of schizophrenia but do not yet have a lot of research behind them. Further controlled trials are needed are needed investigating these newer therapies.

Finally, meta-analyses examining outcomes other than symptom reduction is also warranted. Many mental health services are now interested, and set key performance indicators in, more broad measures of wellbeing such as quality of life (Pilling et al., 2002, Rector & Beck, 2012), medication compliance (Rector & Beck, 2012; Newton-Howes & Wood, 2013), social skills (Pfmatter et al. 2006; Kurtz & Richardson; 2012) and benefits in other areas of community and psychosocial functioning (Kurtz & Richardson, 2012). Therefore investigating the pooled effect of CBT and other treatments on these outcomes is also important in the future.

Conclusion

This study examined the effectiveness of CBT on symptom reduction in schizophrenia, and found small and largely not significant effect sizes for various types of symptoms. When examining moderators, the quality of the trial did have some impact, with higher quality trials resulting in lower effect sizes for general psychopathology and negative symptoms. The number of comprehensiveness of the CBT offered did not alter the effect of the treatment. The use of a manualized treatment was not superior to those who used non-manualised treatment protocols. CBT was no more effective for acute presentations than chronic presentations of the illness, though there was a significant difference in favor of chronic stages for general psychopathology symptoms. The type of control group used only impacted the results for the reduction of general psychopathology symptoms, with smaller effect sizes found when implementing an active control. Finally, individual treatment

was only superior to group treatment modalities for the reduction of negative symptoms. In summary, effect sizes remain small, and moderating effects are inconsistent in determining effective use of CBT for schizophrenia. Though CBT has been recommended as a therapy of choice by peak bodies such as the National Institute of Health and Care Excellence (NICE) and the Royal Australian and New Zealand College of Psychiatrists (NICE, 2014; McGorry, 2005) CBT is not being widely used by mental health services (Wykes et al., 2008). CBT however remains the most researched and the most evidence-based treatment for schizophrenia and psychosis. More study into effective components of CBT and symptom specific areas of focus for CBT is recommended to determine the most effective use of CBT for this population.

References

Acarturk, C., Cuijpers, P., van Straten, A., & de Graaf, R. (2009). Psychological treatment of social anxiety disorder: A meta-analysis. *Psychological Medicine, 39 (2),* 241-254. doi: http://dx.doi.org/10.1017/S0033291708003590

Ale, C. M., McCarthy, D. M., Rothschild, L. M., & Whiteside, S. P. H. (2015). Components of cognitive behavioral therapy related to outcome in childhood anxiety disorders. *Clinical Child and Family Psychology Review, 18 (3),* 240-251. doi: 10.1007/s10567-015-0184-8

AlFaraj, A. M., AlHaddad, M. K., Al-Shboul Q., Qaheri, S., Al-Sadadi, A., Grealy, M., & Al-Nasheet, F. (2006). Prevalence of positive and negative symptoms of schizophrenia. *Journal of the Bahrain Medical Society, 18(4),* 179-183.

Amador, X. F., & Kronengold, H. (2004). Understanding and assessing insight. In X. F. Amador & A. S. David (Eds.), *Insight and Psychosis: Awareness of Illness in Schizophrenia and Related Disorders* (2nd Edition). New York: Oxford University Press.

American Psychiatric Association. (2000) *Diagnostic and statistical manual of mental disorders: DSM IV-TR/* Washington DC: Author

American Psychiatric Association. (2013) *Diagnostic and statistical manual of mental disorders (*5th ed.). Washington DC: Author.

Andreasen, N. C. (1995). Symptoms, signs and diagnosis of schizophrenia. *The Lancet, 346,* 477-481. doi: 10.1016/S0140-6736(95)91325-4

Andrews, J. L., & Fernandez-Enright, F. (2015). Genetic variants in nogo receptor signaling pathways may be associated with early life adversity in

schizophrenia susceptibility. *BBA Clinical, 3,* 36-43. doi: 10.1016/j.bbacli.2014.11.008

Arnold, S.E. (1999). Neurodevelopmental abnormalities in schizophrenia: insights from neuropathology. *Developmental Psychopathology, 11(3),* 439-456. doi: 10.1017/S095457949900214X

Australian Institute of Health and Welfare (2001). Mental health services in Australia 1998-1999: National minimum data sets-Mental health care. Canberra: AIHW.

Australian Institute of Health and Welfare (2005). Mental health services in Australia 2002-2003. Canberra: AIHW.

Australian Institute of Health and Welfare (2014). Mental Health Services: In Brief. Canberra: AIHW.

Bach, P., & Hayes, S. C. (2002). The use of acceptance and commitment therapy to prevent the re-hospitalization of psychotic patients: A randomized controlled trial. *Journal of Consulting and Clinical Psychology, 70,* 1129-1139. doi: 10.1037//0022-006X.70.5.1129

Bangel, F. N., Yamada, K., Arai, M., Iwayama, I., Balan, S., Toyota, T., Iwata, Y., Suzuki, K., Kikuchi, M., Hashimoto, T., Kanahara, N., Mori, N., Itokawa, M., Stork, O., Yoshikawa, T. (2015). Genetic analysis of the glyoxalase system in schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 59,* 105-110. doi: 10.1016/j.pnpbp.2015.01.014

Barrowclough, C., Haddock, G., Lobban, F., (...), Roberts, C., Gregg, L. (2006). Group cognitive-behavioural therapy for schizophrenia: Randomised controlled trial. *British Journal of Psychiatry, 189 (6),* 527-532. doi: 10.1192/bjp.bp.106.021386

Barrowclough, C., Haddock, G., Wykes, T., (...), Steel, C., Tarrier, N. (2010). Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: Randomised controlled trial. *British Medical Journal, 341 (24),* 6325. doi: 10.1136/bmj.c6325

Bauer, S. M., Schanda, H., Karakula, H., Olajossy-Hilkesberger, L., Rudaleviciene, P., Okribelashvili, N., Chaudry, H. R., Idemudia, S. E., Gscheider, S., Ritter, K., & Stompe, T. (2011). Culture and the prevalence of hallucinations in schizophrenia. *Comprehensive Psychiatry*, *52,* 319-325. doi: 10.1016/j.comppsych.2010.06.008

Bechdolf, A., Köhn, D., Knost, B., Pukrop, R., Klosterkötter, J. (2005). A randomized comparison of group cognitive-behavioural therapy and group psychoeducation in acute patients with schizophrenia: Outcome at 24 months. *Acta Psychiatrica Scandinavica, 112 (3),* 173-179. doi: 10.1111/j.1600-0447.2005.00581.x

Begg, C. B., & Mazumdar, M. (1994). Operating Characteristics of a Rank Correlation Test for Publication Bias. *Biometrics, 50*(4), 1088-1101. doi: 10.2307/2533446

Benes, F. M. (2000). Emerging principles of altered neural circuitry in schizophrenia. *Brain Research Reviews, 31(2-3),* 251-269. doi: 10.1016/S0165-0173(99)00041-7

Bobes, J., Arango, C., Garcia-Garcia, M., & Rejas, J. (2010). Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antispsychotics in routine clinical practice: Findings from the CLAMORS study. *Journal of Clinical Psychiatry, 71(3),* 280-286. doi: 10.4088/JCP.08m04250yel

Borenstein, M., Hedges, L.V., Higgins, J. P. T., Rothstein, H. R. (2009). *Introduction to Meta-Analysis.* Chichester, UK: John Wiley & Sons, Ltd.

Brabban, A., Tai, S., & Turkington, D. (2009). Predictors of outcome in brief cognitive behaviour therapy for schizophrenia. *Schizophrenia Bulletin, 35,* 859-864. doi: 10.1093/schbul/sbp065

Breier, A., & Berg, P. H. (1999). The psychosis of schizophrenia: Prevalence, response to atypical antipsychotics, and prediction of outcome. *Biological Psychiatry, 46(3),* 361-364. doi: 10.1016/S0006-3223(99)00040-2

Brown, A. S., Begg, M. D., Gravenstein, S., Shaefer, C. A., Wyatt, R. J., Bresnahan, M., Babulas, V. P. & Susser, E. S. (2004). Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Archives of General Psychiatry, 61,* 774-780. doi:10.1001/archpsyc.61.8.774

Brown, A. S., Cohen, P., Harkavy-Friedman, J., Babulas, V. (2001). Prenatal rubella, premorbid abnormalities, and adult schizophrenia. *Biological Psychiatry, 49,* 473-486. doi: 10.1016/S0006-3223(01)01068-X

Bryant, R. A., Moulds, M. L., Guthrie, R. M., Dang, S. T., & Nixon, R. D. V. (2003). Imaginal exposure alone and imaginal exposure with cognitive restructuring in treatment of posttraumatic stress disorder. *Journal of*

Consulting and Clinical Psychology, 71, 706-712. doi:10.1037/0022-006X.71.4.706

Buchanan, R.W., Kreyenbuhl, J., Kelly, D. L., Noel, J. M., Boggs, D. L., Fischer, B. A., Himelhoch, S., Fang, B., Peterson, E., Aquino, P. R., & Keller, W. (2010). The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements. *Schizophrenia Bulletin, 36 (1):* 71-93. doi: 10.1093/schbul/sbp116

Burns, A. M. N., Erickson, D. H., & Brenner, C. A. (2014). Cognitive-behavioral therapy for medication-resistant psychosis: A meta-analytic review. *Psychiatric Services, 65 (7),* 874-880. doi: 10.1176/appi.ps.201300213

Cannon, T. D., Rosso, I. M., Hollister, J. M., Bearden, C. E., Sanchez, L. E., & Hadley, T. (2000). A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. *Schizophrenia Bulletin, 26(2),* 351-366. doi: 10.1093/oxfordjournals.schbul.a033458

Cannon, T. D., van Erp, T. G., Rosso, I. M., Huttunen, M., Lönnqvist, J., Pirkola, T., Salonen, O., Valanne, L., Poutanen, V., Standertskjöld-Nordenstam, C. (2002). Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. *Archives of General Psychiatry, 59 (1),* 35-41. doi:10.1001/archpsyc.59.1.35

Cantor-Graae, E., Selten, J. (2005). Schizophrenia and migration: A meta-analysis and review. *The American Journal of Psychiatry, 162 (1),* 12-24. doi: 10.1176/appi.ajp.162.1.12

Cardno, A. G., & Gottesman, I. I. (2000). Twin studies of schizophrenia: From bow-and-arrow concordances to star wars Mx and functional genomics. *American*

Journal of Medical Genetics, 97 (1), 12-17. doi: 10.1002/(SICI)1096-8628(200021)97:1<12::AID-AJMG3>3.0.CO;2-U

Carlsson, A., Waters, N., Holm-Waters, S., Tedroff, J., Nilsson, M., & Carlsson, M. L. (2001). Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annual Review of Pharmacological Toxicology, 41,* 237-260. doi: 10.1146/annurev.pharmtox.41.1.237

Castonguay, L. G., Goldfried, M. R., Wiser, S., Raue, P. J., & Hayes, A. M. (1996). Predicting the effect of cognitive therapy for depression: A study of unique and common factors. *Journal of Consulting and Clinical Psychology, 64 (3),* 407-504. doi: 10.1037/0022-006X.64.3.497

Cather, C., Penn, D., Otto, M. W., (...), Mueser, K. T., Goff, D. C. (2005). A pilot study of functional cognitive behavioral therapy (fCBT) for schizophrenia. *Schizophrenia research, 74 (2-3),* 201-209. doi: 10.1016/j.schres.2004.05.002

Chen, E., Touyz, S. W., Beumont, P. J. V., Fairburn, C. G., Griffiths, R., Butow, P., Russell, J., Schotte, D. E., Gertler, R., & Basten, C. Comparison of group and individual cognitive-behavioral therapy for patients with bulimia nervosa. *International Journal of Eating Disorders, 33 (3),* 241-254. doi: 10.1002/eat.10137

Ciompi, L. (1980). The natural history of schizophrenia in the long-term. *British Journal of Psychiatry, 136,* 413-20. doi: 10.1192/bjp.136.5.413

Clark, D. M. (1986). A cognitive approach to panic. *Behaviour Research and Therapy, 24,* 461-470. doi:10.1016/0005-7967(86)90011-2

Close, H., & Schuller, S. (2004). Psychotic symptoms. In: Bennett-Levy, J., Butler, G., Fennell, M., Hackmann, A., Mueller, M., & Westbrook, D. (Eds.). *Oxford guide to behavioural experiments in cognitive therapy*, pp. 245-263.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd Ed.). Hillsdale: Lawrence Erlbaum Associates.

Comprehensive Meta-Analysis (Version 2) [Computer software]. (2014). Englewood, NJ: Biostat. Available from http://www.comprehensive.com

Connolly Gibbons, M.B., Crits-Christoph, P., Levinson, J., Barber, J. (2003). Flexibility in manual-based psychotherapies: Predictors of therapist interventions in interpersonal and cognitive-behavioral therapy. *Psychotherapy Research, 13 (2),* 169-185. doi: 10.1093/ptr/kpg017

Copeland, M. E. (1997). *Wellness Recovery Action Plan*. United States: Rittenhouse.

Crowe, T. J. (1990). Temporal lobe asymmetries as the key to the etiology of schizophrenia. *Schizophrenia Bulletin, 16(3),* 433-443. doi: 10.1093/schbul/16.3.433

David, A., & Prince, M. (2005). Psychosis following head injury: A critical review. *Journal of Neurology, Neurosurgery and Psychiatry, 76 (suppl 1),* i53-i60. doi:10.1136/jnnp.2004.060475

Davis, K. L., Kahn, R. S., Ko, G., Davidson, M. (1991). Dopamine in schizophrenia: A review and reconceptualization. *American Journal of Psychiatry, 148(11),* 1474-1486. http://dx.doi.org/10.1176/ajp.148.11.1474

Dickerson, F. B., Lehman, A. F. (2011). Evidence-Based Psychotherapy for Schizophrenia: 2011 Update. *The Journal of Nervous and Mental Disease, 199 (8),* 520-526. doi: 10.1097/NMD.0b013e318225ee78

Dimidjian, S., Hollon, S. D., Dobson, K. S., Schmaling, K. B., Kohlenberg, R. J., Addis, M. E., . . . Jacobson, N. S. (2006). Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute

treatment of adults with major depression. *Journal of Consulting and Clinical Psychology, 74*(4), 658-670. doi:http://dx.doi.org/10.1037/0022-006X.74.4.658

Dudley, R., Bryant, C., Hammond, K., Siddle, R., Kingdon, D., & Turkington, D. (2007). Techniques in cognitive behavioural therapy: Using normalizing in schizophrenia. *Journal of the Norwegian Psychological Association, 44,* 562-572. doi: http://eprints.soton.ac.uk/id/eprint/62366

Dunn, G., Fowler, D., Rollinson, R., (...), Garety, P., Bebbington, P (2012). Effective elements of cognitive behaviour therapy for psychosis: Results of a novel type of subgroup analysis based on principal stratification. *Psychological Medicine, 42 (5),* 1057-1068. doi: 10.1017/S0033291711001954

Durham, R. C., Guthrie, M., Morton, R. V., Reid, D. A., Treliving, L., Fowler, D., & Macdonald, R. (2003). Tayside-Fyfe clinical trial of cognitive-behavioural therapy for medication-resistant psychotic symptoms: Results to 3-month follow up. *British Journal of Psychiatry, 182,* 303-311. doi: 10.1192/bjp.182.4.303

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics, 56 (2),* 455-463. doi: 10.2307/2676988

Egger, M., Davey-Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ : British Medical Journal, 315 (7109),* 629–634. doi: 10.1136/bmj.315.7109.629

Ehlers, A., Hackmann, A., Grey, N., Wild, J., Liness, S., Albert, I., Deale, A., Stott, R., & Clark, D. M. (2014). A randomized controlled trial of 7-day intensive and standard weekly cognitive therapy for PTSD and emotion-focused

supportive therapy. *American Journal of Psychiatry*, *171*, 294-304. doi: 10.1176/appi.ajp.2013.13040552

Ekers, D., Webster, L., Van Straten, A., Cuijpers, P., Richards, D., & Gilbody, S. (2014). Behavioural activation for depression: An update of meta-analysis of effectiveness and sub group analysis. *PLoS ONE*, *9(6)*, e100100. doi: http://doi.org/10.1371/journal.pone.0100100

Foa, E. B., Liebowitz, M. R., Kozak, M. J., (...), Simpson, H. B., & Tu, X. (2005). Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. *American Journal of Psychiatry, 162,* 151-161. doi: 10.1176/appi.ajp.162.1.151

Fowler, D. F., Garety, P., & Kuipers, E. (1995). *Cognitive Behaviour Therapy for Psychosis: Theory and Practice.* Chichester: John Wiley & Sons.

Gaudiano, B. A., & Herbert, J. D. (2006). Acute treatment of inpatients with psychotic syptoms using acceptance and commitment therapy: Pilot results. *Behaviour Research and Therapy, 44,* 415-437. doi:10.1016/j.brat.2005.02.007

Giezendanner, S., Walther, S., Razavi, N., Van Swam, C., Fisler, M. S., Soravia, L. M., . . . Federspiel, A. (2013). Alterations of white matter integrity related to the season of birth in schizophrenia: A DTI study. *PLoS ONE*, *8(9)*, e75508. doi:10.1371/journal.pone.0075508

Goff, D. C., & Coyle, J. T. (2001). The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *The American Journal of Psychiatry, 158 (9),* 1367-1377. doi: 10.1176/appi.ajp.158.9.1367

Grace, A. A. (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia. *Neuroscience, 41 (1),* 1-24. doi: 10.1016/0306-4522(91)90196-U

Granholm, E., Holden, J., Link, P. C., & McQuaid, J. R. (2014). Randomized clinical trial of cognitive behavioral social skills training for schizophrenia: Improvement in functioning and experiential negative symptoms. *Journal of Consulting and Clinical Psychology, 82 (6),* 1173-1185. doi: 10.1037/a0037098

Granholm, E., Holden, J., Link, P. C., McQuaid, J. R., & Jeste, D. V. (2013). Randomized controlled trial of cognitive behavioral social skills training for older consumers with schizophrenia: Defeatist performance attitudes and functional outcome. *The American Journal of Geriatric Psychiatry, 21 (3),* 251-262. doi: 10.1016/j.jagp.2012.10.014

Gumley, A., O'Grady, M., McNay, L., (...), Power, K., Norrie, J. (2003). Early intervention for relapse in schizophrenia: Results of a 12-month randomized controlled trial of cognitive behavioural therapy. *Psychological Medicine, 33 (3),* 419-431. doi: 10.1017/S0033291703007323

Haddock, G., Tarrier, N., Morrison, A. P., (...), Lewis, S., Haddock, G.(1999). A pilot study evaluating the effectiveness of individual inpatient cognitive-behavioural therapy in early psychosis. *Social Psychiatry and Psychiatric Epidemiology, 34 (5),* 254-258. doi: 10.1007/s001270050141

Haddock, G., Barrowclough, C., Shaw, J. J., (...), Novaco, R. W., Tarrier, N. (2009). Cognitive-behavioural therapy v. social activity therapy for people with psychosis and a history of violence: Randomised controlled trial. *British Journal of Psychiatry, 194 (2),* 152-157. doi: 10.1192/bjp.bp.107.039859

Häfner, H., Maurer, K., Löffler, W., (...), Behrens, S., Gattaz, W. F. (1994). The epidemiology of early schizophrenia. Influence of age and gender on onset and early course. *British Journal of Psychiatry, Supplement, 23,* 29-38.

Hans, E., & Hiller, W. (2013). Effectiveness of and dropout from outpatient cognitive behavioral therapy for adult unipolar depression: a meta-analysis of nonrandomized effectiveness studies. *Journal of Consulting and Clinical Psychology, 81 (1),* 75-88.

Harrow, M., Sands, J. R., Silverstein, M. L., & Goldberg, J. F. (1997). Course and outcome for schizophrenia versus other psychotic patients: A longitudinal study. *Schizophrenia Bulletin, 23 (2),* 287-303. doi: 10.1093/schbul/23.2.287

Harvey, P. D., Lombardi, J., Leibman, M., (...), Davidson, M., Davis, K. L. (1997). Age-related differences in formal thought disorder in chronically hospitalized schizophrenic patients: A cross-sectional study across nine decades. *American Journal of Psychiatry, 154 (2),* 205-210.

Hedman, E., Mörtberg, E., Hesser, H., Clark, D. M., Lekander, M., Andersson, E., & Ljótsson, B. (2013). Mediators in psychological treatment of social anxiety disorder: Individual cognitive therapy compared to cognitive behavioral group therapy. *Behaviour Research and Therapy, 51 (10),* 696-705. doi: 10.1016/j.brat.2013.07.006

Herbert, R. D., & Bø, K. (2005). Analysis of quality of interventions in systematic reviews. *British Medical Journal, 331 (7515),* 507-509.

Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal, 327 (7414),* 557-560. doi: 10.1136/bmj.327.7414.557

Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: Version III—The final common pathway. *Schizophrenia Bulletin, 35 (3),* 549-562. doi: 10.1093/schbul/sbp006

Jackson, H. J., McGorry, P. D., Killackey, E., (...), Johnson, T., & Harrigan, S. (2008). Acute-phase and 1-year follow-up results of a randomized controlled trial of CBT versus befriending for first-episode psychosis: The ACE project. *Psychological medicine, 38 (5),* 725-735. doi: 10.1017/S0033291707002061

Jauhar, S., McKenna, P. J., Radua, J., (...), Salvador, R., Laws, K. R. (2014). Cognitive-behavioural therapy for the symptoms of schizophrenia: Systematic review and meta-analysis with examination of potential bias. *British Journal of Psychiatry, 204 (1),* 20-29. doi: 10.1192/bjp.bp.112.116285

Johnsen, T. J., & Friborg, O. (2015). The effects of cognitive behavioral therapy as an anti-depressive treatment is falling: A meta-analysis. *Pscyhological Bulletin, 141 (4),* 747-768. doi: 10.1037/bul0000015

Jones, C., Hacker, D., Cormac, I., Meaden, A., & Irving, C. B. (2012). Cognitive behaviour therapy versus other psychosocial treatments for schizophrenia. *Cochrane Database of Systematic Reviews, 4,* Retrieved from:

http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/index.html

Kemp, R., Kirov, G., Everitt, B., Hayward, P., & David, A. (1998). Randomized controlled trial of compliance therapy, 18 month follow-up. *British Journal of Psychiatry, 172,* 413-419.

Kennard, B. D., Clarke, G. N., Weersing, V. R., Asarnow, J, R., Shamseddeen, W., Porta, G., Berk, M., Hughes, J. L., Spirito, A., Emslie, G. J., Keller, M. B., Wagner, K. D., Brent, D. A. (2009). Effective components of TORDIA cognitive-behavioral therapy for adolescent depression: Preliminary findings. *Journal of Consulting and Clinical Psychology, 77 (6),* 1033-1041. doi: 10.1037/a0017411

Kestler, L. P., Walker, E., & Vega, E. M. (2001). Dopamine receptors in the brains of schizophrenia patients: A meta-analysis of the findings. *Behavioural Pharmacology, 12 (5),* 355-371.

Killackey, E., Krstev, H., & Gleeson, J. F. M. (2008). Psychosocial interventions in clinical practice guidelines for schizophrenia. In J. F. M. Gleeson, E. Killackey, & H. Krstev. (Eds). *Psychotherapies for the Psychoses: Theoretical, Cultural and Clinical Integration.* Melbourne: Routledge. doi: 10.4324/9780203937976

Knuts, I. J., Esquivel, G., Overbeek, T., & Schruers, K. R. (2015). Intensive behavioral therapy for agoraphobia. *Journal of Affective Disorders, 174,* 19-22. doi: 10.1016/j.jad.2014.11.029

Krabbendam, L., & van Os, J. (2005). Schizophrenia and urbanicity: A major environmental influence- Conditional on genetic risk. *Schizophrenia Bulletin, 31 (4),* 795-799. doi: 10.1093/schbul/sbi060

Kuipers, E. K., Garety, P. A., Fowler, D., Dunn, G., Bebbington, P., Freeman, D & Hadley, C. (1997). London-East Anglia randomized controlled trial of cognitive-behavioural therapy for psychosis. I: Effects of the treatment phase. *British Journal of Psychiatry, 171,* 319-327.

Kuipers, E., Holloway, F., Rabe-Hesketh, S., Tennakoon, L. (2004). An RCT of early intervention in psychosis: Croydon Outreach and Assertive Support Team (COAST). *Social Psychiatry and Psychiatric Epidemiology, 39 (5),* 358-363. doi: 10.1007/s00127-004-0754-4

Kurtz, M. M., & Richardson, C. L. (2012). Social cognitive training for schizophrenia: A meta-analytic investigation of controlled research. *Schizophrenia Bulletin, 38 (5),* 1092-1104. doi: 10.1093/schbul/sbr036

Lacro, J. P., Dunn, L. B., Dolder, C. R., Leckband, S. G., & Jeste, D. V. (2002). Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: A comprehensive review of recent literature. *Journal of Clinical Psychiatry, 63 (10),* 892-909.

Larson, M. K., Walker, E. F., & Compton, M. T. (2010). Early signs, diagnosis and therapeutics of the prodromal phase of schizophrenia and related psychotic disorders. *Expert Review of Neurotherapeutics, 10 (8),* 1347-1359. doi: 10.1586/ern.10.93

Lawrie, S. M., & Abukmeil, S. S. (1998). Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry, 172,* 110-120.

Lepage, L., Altman, D. G., Schulz, K. F., Moher, D., Egger, M., Davidoff, F., . . . Lang, T. (2001). The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Annals of Internal Medicine, 134*(8), 663-694. Retrieved from http://www.scopus.com/inward/record.url?eid=2-s2.0-0035901579&partnerID=40&md5=401f7dc89dd6f38ac9cc0c63ff7d0936

Lewis, S., Tarrier, N., Haddock, G., (...), Faragher, B., Dunn, G. (2002). Randomised controlled trial of cognitive-behavioural therapy in early schizophrenia: Acute-phase outcomes. *British Journal of Psychiatry, 181 (43)*, s91-s97.

Li, Z.-J., Guo, Z.-H., Wang, N., (...), Turkington, D., & Kingdon, D. (2014). Cognitive–behavioural therapy for patients with schizophrenia: A multicentre randomized controlled trial in Beijing, China. *Psychological Medicine, 45 (9),* 1893-1905. doi: 10.1017/S0033291714002992

Lincoln, T. M., Ziegler, M., Mehl, S., (...), Westermann, S., & Rief, W. (2012). Moving from efficacy to effectiveness in cognitive behavioral therapy for psychosis: A randomized clinical practice trial. *Journal of Consulting and Clinical Psychology, 80 (4),* 674-686. doi: 10.1037/a0028665

Lindenmayer, J. P. (2000). Treatment refractory schizophrenia. *Psychiatric Quarterly, 71 (4),* 373-384. doi: 10.1023/A:1004640408501

Lindström, L. H., Gefvert, O., Hagberg, G., (...), Hartvig, P., Långström, B. (1999). Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(β-11C) DOPA and PET. *Biological Psychiatry, 46 (5),* 681-688. doi: 10.1016/S0006-3223(99)00109-2

Liu, H., Fu, Y., Ren, J., (...), Dong, Y., Li, H. (2015). Association between NR4A2 genetic variation and schizophrenia: A comprehensive systematic review and

meta-analysis. *Neuroscience Letters, 598,* 85-90. 10.1016/j.neulet.2015.05.018

Marwaha, S., & Johnson, S. (2004). Schizophrenia and employment: A review. *Social Psychiatry and Psychiatric Epidemiology, 39 (5),* 337-349. doi: 10.1007/s00127-004-0762-4

Matsumoto, K., Hamaie, Y., Mitsunaga, N., Uchida, T., Sunakawa, E., Ohmuro, N., Katsura, M., & Matsuoka, H. (2013). Application of cognitive behavioral therapy to early phase of psychosis. *Psychiatria et Neurologia Japonica, 115 (4).* 390-398.

McGorry, P. (2005). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. *Australian & New Zealand Journal of Psychiatry, 39 , (1-2),* 1-30. doi: 10.1111/j.1440-1614.2005.01516.x

McGorry, P., Killackey, E., Elkins, K., Lambert, M., & Lambert, T. (2003). Summary Australian and New Zealand clinical practice guideline for the treatment of schizophrenia. *Australasian Psychiatry, 11 (2),* 136-147. doi: 10.1046/j.1039-8562.2003.00535.x

McNeil, T. F., Cantor-Graae, E., & Ismail, B. (2000). Obstetric complications and congenital malformation in schizophrenia. *Brain Research Reviews, 31 (2-3),* 166-178. doi: 10.1016/S0165-0173(99)00034-X

Minjoo, K., Mpofu, E., Brock, K., Millington, M., & Athanasou, J. (2014). Cognitive-behavioural therapy effects on employment-related outcomes for individuals with mental illness: A systematic review. *SA Journal of Industrial Psychology, 40 (2),* 1-6. doi: 10.4102/sajip.v40i2.1188

Minozzi, S., Davoli, M., Bargagli, A. M., Amato, L., Vecchi, S., Perucci, C. A. (2010). An overview of systematic reviews on cannabis and psychosis: Discussing apparently conflicting results. *Drug and Alcohol Review, 29,* 304-317. doi: 10.1111/j.1465-3362.2009.00132.x

Miyamoto, S., Duncan, G. E., Marx, C. E., & Lieberman, J. E. (2005). Treatments for schizophrenia: A critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular Psychiatry, 10,* 79-104. doi:10.1038/sj.mp.4001556

Möller, M., Swanepoel, & Harvey, B. H. (2015). Neurodevelopmental animal models reveal the convergent role of neurotransmitter systems, inflammation, and oxidative stress as biomarkers of schizophrenia: Implications for novel drug development. *ACS Chemical Neuroscience, 6,* 987-1016. doi: 10.1021/cn5003368.

Molloy, C., Conroy, R. M., Cotter, D. R., Cannon, M. (2011). Is traumatic brain injury a risk factor for schizophrenia? A meta-analysis of case-controlled population-based studies. *Schizophrenia Bulletin, 37 (6),* 1104-1110. doi: 10.1093/schbul/sbr091

Morgan, V. A., Valuri, G. M., Croft, M. L., Griffith, J. A., Shah, S., Young, D. J., Jablensky, A. V. (2011). Cohort profile: Pathways of risk from conception to disease: the Western Australian schizophrenia high-risk e-Cohort. *International Journal of Epidemiology, 40 (6),* 1477-1485. doi: 10.1093/ije/dyq167

Morgan, C., & Fisher, H. (2007). Environment and schizophrenia: Environmental factors in schizophrenia: Childhood trauma—A critical review. *Schizophrenia Bulletin, 33 (1),* 3-10. *doi: 10.1093/schbul/sbl053*

Morrison, A. P. (2001). The interpretation of intrusions in psychosis: An integrative cognitive approach to hallucinations and delusions. *Behavioural and Cognitive Psychotherapy, 29 (3),* 257-276. doi: 10.1017/S1352465801003010

Morrison, A. P., Nothard, S., Bowe, S. E., Wells, A. (2004). Interpretations of voices in patients with hallucinations and non-patient controls: A comparison and predictors of distress in patients. *Behaviour Research and Therapy, 42 (11),* 1325-1323. doi: 10.1016/j.brat.2003.08.009

Moritz, S., Veckenstedt, R., Randjbar, S., Vitzthum, F. & Woodward, T. S. (2011). Antipsychotic treatment beyond antipsychotics: Metacognitive intervention for schizophrenia patients improves delusional symptoms. *Psychological Medicine, 41 (9),* 1823-1832. doi:10.1017/S0033291710002618

Moritz, S., Vitzthum, F., Randjbar, S., Veckenstedt, R., & Woodward, Todd S. (2010). Detecting and defusing cognitive traps: metacognitive intervention in schizophrenia. *Current Opinion in Psychiatry. 23(6),* 561-569. doi:10.1097/YCO.0b013e32833d16a8.

National Institute for Health and Care Excellence. (2014). *Psychosis and Schizophrenia in Adults: Treatment and Management*. London: NICE.

Newton-Howes, G., Wood, R. (2013). Cognitive behavioural therapy and the psychopathology of schizophrenia: Systematic review and meta-analysis.

Psychology and Psychotherapy, 86 (2), 127-138. doi: 10.1111/j.2044-8341.2011.02048.x

Nothard, S., Morrison, A. P., & Wells, A. (2008). Identifying specific interpretations and exploring the nature of safety behaviours for people who hear voices: An exploratory study. *Behavioural and Cognitive Psychotherapy, 36(3),* 353-357. doi: 10.1017/S1352465808004372

O'Callaghan, E., Gavin, B., Cullen, W.. O'Donoghue, B., Ascencio-Lane, J., Bury, G. (2006). First episode schizophrenia in general practice: A national study. *Irish Journal of Psychological Medicine, 23(1),* 6-9.

O'Donnell, C., Donohoe, G., Sharkey, L., Owens, N., Migone, M., Harries, R., Kinsella, A., Larkin, C., & O'Callaghan, E. (2003). Compliance therapy: A randomised controlled trial in schizophrenia. *British Medical Journal, 327:* 834.

Pearlson, G. D., Kim, W. S., Kubos, K. L., Moberg, P. J., Jarayam, G., Bascom, M. J., Chase, G. A., Goldfinger, A. D., & Tune, L. E. (1989). Ventricle-brain ratio, computed tomographic density, and brain area in 50 schizophrenics. *Archives of General Psychiatry, 46,* 690-697. doi:10.1001/archpsyc.1989.01810080020003

Peters, E., Landau, S., McCrone, P., (...), Howard, A., Kuipers, E. (2010). A randomised controlled trial of cognitive behaviour therapy for psychosis in a routine clinical service. *Acta Psychiatrica Scandinavica, 122 (4),* 302-318. doi: 10.1111/j.1600-0447.2010.01572.x

Pfammatter, M., Junghan, U. M., & Brenner, H. D. (2006). Efficacy of psychological therapy in schizophrenia: Conclusions from meta-analyses. *Schizophrenia Bulletin, 32* (SUPPL.1), S64-S80.

Pilling, S., Bebbington, P., Kuipers, E., Garety, P., Geddes, J., Orbach, G., & Morgan, C. (2002). Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. *Psychological Medicine, 32,* 763-782. doi: 10.1017/S0033291702005640

Pinto, A., La Pia, S., Mennella, R., Giorgio, D., & DeSimone, L. (1999). Cogntive-behavioural therapy and clozapine for clients with treatment-refractory schizophrenia. *Psychiatric Services, 50(7),* 901-904.

Potash, J. B., Willour, V. L., Chiu, Y. F., Simpson, S. G, MacKinnon, D. F., Pearlson, G. D., DePaulo, J. R, & McInnis, M. G. (2001). The familial aggregation of psychotic symptoms in bipolar disorder pedigrees. *American Journal of Psychiatry, 158(8),* 1258-1264. doi: 10.1176/appi.ajp.158.8.1258

Raune, D., Kuipers, E., & Bebbigton, P. (2009). Stressful and intrusive life events preceeding first episode psychosis. *Epidemiologica e Psichiatria Sociale, 18(3),* 221-228.

Rector, N. A., & Beck, A. T. (2001). Cognitive behavioral therapy for schizophrenia: An empirical review. *The Journal of Nervous and Mental Disease, 189 (5),* 278-287. doi: 10.1097/00005053-200105000-00002

Rector, N. A., & Beck, A. T. (2012). Cognitive behavioral therapy for schizophrenia: An empirical review. *The Journal of Nervous and Mental Disease, 200 (10),* 832-839. doi: 10.1097/NMD.0b013e31826dd9af

Riecher-Rossler, A., & Hafner, H. (2000). Gender aspects in schizophrenia: Bridging the border between social and biological psychiatry. *Acta Psychiatrica Scandinavia, 102 (407),* 58-62.

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J. L., Kähler, A. K., Akterin, S., . . . Sullivan, P. F. (2013). Genome-wide Association Analysis Identifies 14 New Risk Loci for Schizophrenia. *Nature Genetics, 45(10),* doi:10.1038/ng.2742

Rollinson, R., Smith, B., Steel, C., Jolley, S., Onwumere, J., Garety, P. A., Kuipers, E., Freeman, D., Bebbington, P. E., Dunn, G., Startup, M., & Fowler, D. (2008). Measuring adherence for CBT in psychosis: A Psychometric analysis of a psychometric scale. *Behavioural and Cognitive Psychotherapy, 36,* 163-178. doi: 10.1017/S1352465807003980

Rule, A. (2005). Ordered thoughts on thought disorder. *Psychiatric Bulletin, 29,* 462-464. doi: 10.1192/pb.29.12.462

SANE Australia (2002). *Schizophrenia: Costs. An analysis of the burden of schizophrenia and related suicide in Australia*. Melbourne: SANE Australia.

Sarin, F., Wallin, L., & Widerlöv, B. (2011). Cognitive behavior therapy for schizophrenia: A meta-analytical review of randomized controlled trials. *Nordic Journal of Psychiatry, 65,* 162-174. doi: 10.3109/08039488.2011.577188

Schmajuk, N.A. (2001). Hippocampal dysfunction in schizophrenia. *Hippocampus, 11(5),* 599-613. doi: 10.1002/hipo.1074

Schulte, D., Künzel, R., Pepping, G., & Schulte-Bahrenberg, T. (1992). Tailor-made versus standardized therapy of phobic patients. *Advances in Behaviour Research and Therapy, 14(2),* 67-92. doi: 10.1016/0146-6402(92)90001-5

Sensky, T., Turkington, D., Kingdon, D., Scott, J. L., Scott, J., Siddle, R., O'Carroll, M., & Barnes, T. R. (2000). A randomized control trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Archives of General Psychiatry, 57(2),*165-172.

Sery, O., Lochman, J., Povova, J., Janout, V., Plesnik, J., & Balcar, V. J. (2015). Assocation between 5q23.2-located polymorphism of *CTXN3* gene (Cortexin 3) and schizophrenia in European-Caucasian males: Implications for the aetiology of schizophrenia. *Behavioral and Brain Functions, 11 (10),* doi: 10.1186/s12993-015-057-9.

Shafran, R., Clark, D. M., Fairburn, C. G., Arntz, A., Barlow, D. H., Ehlers, A., …Wilson, G. T. (2009). Mind the gap: Improving the dissemination of CBT. *Behaviour Research and Therapy, 47,* 902-909. http://dx.doi.org/10.1016/j.brat.2009.07.003.

Sharpless, B. A., & Barber, J. P. (2009). A conceptual and empirical review of meaning, measurement, development and teaching of intervention competence in clinical psychology. *Clinical Psychology Review, 29,* 47-56. doi: 10.1016/j.cpr.2008.09.008

Schulz, K. F., Altman, D. G., & Moher, D.(2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. British Medical Journal, 340, c332. doi: http://dx.doi.org/10.1136/bmj.c332

Sivec, H. J., & Montesano, V. L. (2012). Cognitive behavioral therapy for psychosis in clinical practice. *Psychotherapy, 49(2),* 258-270. doi: 10.1037/a0028256

Stewart, R. E., & Chambless, D. L. (2009). Cognitive–behavioral therapy for adult anxiety disorders in clinical practice: A meta-analysis of effectiveness

studies. *Journal of Consulting and Clinical Psychology*, *77*(4), 595-606. doi:http://dx.doi.org/10.1037/a0016032

Tarrier, N., Lewis, S., Haddock, G., (...), Palmer, S., Dunn, G. (2004). Cognitive-behavioural therapy in first-episode and early schizophrenia: 18-month follow-up of a randomised controlled trial. *British Journal of Psychiatry, 184 (3),* 231-239. doi: 10.1192/bjp.184.3.231

Tarrier, N. (2008). Schizophrenia and other psychotic disorders. In Barlow, D. H (Ed). *Clinical Handbook of Psychological Disorders: A Step-By-Step Treatment Manual.* New York: The Guildford Press. p 463-491.

Tarrier, N., & Wykes, T. (2004). Is there evidence that cognitive-behavioural therapy is an effective treatment for schizophrenia? A cautious or cautionary tale. *Behaviour Research and Therapy, 42,* 1377-1401. doi: 10.1016/j.brat.2004.06.020

Teng, E. J., Barrera, T. L., Hiatt, E. L., (...), Petersen, N. J., & Stanley, M. A. (2015). Intensive weekend group treatment for panic disorder and its impact on co-occurring PTSD: A pilot study. *Journal of Anxiety Disorders, 33,* 1-7. doi: 10.1016/j.janxdis.2015.04.002

Tienari, P., Wynne, L.C., Laksy, K., Moring, J., Nieminen, P., Sorri, A., Lahti, I., & Wahlberg, K-E. (2003). Genetic boundaries of the schizophrenia spectrum: Evidence from the Finnish adoptive family study of schizophrenia. *The American Journal of Psychiatry, 160(9), 1587-1594.* doi: 10.1176/appi.ajp.160.9.1587

Thornicroft, G., & Susser, E. (2001). Evidence-based psychotherapeutic interventions in the community care of schizophrenia. *The British Journal of Psychiatry, 178,* 2-4. doi: 10.1192/bjp.178.1.2

Tsuang, M. T., Stone, W. S., Faraone, S. V. (2000). Towards reformulating a diagnosis for schizophrenia. *The American Journal of Psychiatry, 157 (7),* 1041-1050. http://dx.doi.org/10.1176/appi.ajp.157.7.1041

Turkington, D., & Kingdon, D. (2000). Cognitive-behavioural techniques for general psychiatrists in the management of patients with psychoses. *British Journal of Psychiatry, 177,* 101-106. doi: 10.1192/bjp.177.2.101

Ursano, R. J., Bell, C., Eth, S., Friedman, M., Norwood, A.Pfefferbaum, B., Pynoos, J. D., Zatzick, D. F., Benedek, D. M., McIntyre, J. S., Charles, S. C., Altshuler, K., Cook, I., Cross, C. D., Mellman, L., Moench, L. A., Norquist, G., Twemlow, S. W., Woods, S., & Yager, J.. (2004). Practice guidelines for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *American Journal of Psychiatry, 161*(11), 1-31.

Valmaggia, L. R., Van Der Gaag, M., Tarrier, N., Pijnenborg, M., Slooff, C. J. (2005). Cognitive-behavioural therapy for refractory psychotic symptoms of schizophrenia resistant to atypical antipsychotic medication: Randomised controlled trial. *British journal of psychiatry, 186 (4),* 324-330. doi: 10.1192/bjp.186.4.324

Van Der Gaag, M., Nieman, D. H., Rietdijk, J., Dragt, S., Ising, H. K., Klaassen, R. M. C., Koeter, M., Cuijpers, P., Wunderink, L., & Linszen, D. H. (2012). Cognitive behavioral therapy for subjects at ultrahigh risk for developing psychosis: A randomized controlled clinical trial. *Schizophrenia Bulletin, 38 (6),* 1180-1188. doi: 10.1093/schbul/sbs105

Van Os, J., Kenis, G., & Rutten, B.P.F. (2010). The environment and schizophrenia. *Nature, 468,* 203-212. doi: 10.1038/nature09563

Velthorst, E., Koeter, M., van der Gaag, M., Nieman, D. H., Fett, A.-K. J., Smit, F., Staring, A. B. P., Meijer, C., & de Haan, L. (2015). Adapted cognitive-behavioural therapy required for targeting negative symptoms in schizophrenia: meta-analysis and meta-regression. *Psychological Medicine, 45,* 453-465. doi: 10.1017/S0033291714001147

Volkow, N. D. (2009). Substance use disorders in schizophrenia: Clinical implications of comorbidity. *Schizophrenia Bulletin, 35(3),* 469-472. doi: 10.1093/schbul/sbp016

Walker, E. (1994). Developmentally moderated expressions of the neuropathology underlying schizophrenia. *Schizophrenia Bulletin, 20,* 453-480.

Walker, E., Kestler, L., Bollini, A., & Hochman, K.M. (2004). Schizophrenia: Etiology and course. *Annual Review of Psychology, 55,* 401-430. doi: 10.1146/annurev.psych.55.090902.141950

Westen, D., Morrison, K. (2001). A multidimensional meta-analysis of treatments for depression, panic, and generalized anxiety disorder: An empirical examination of the status of empirically supported therapies . *Journal of Consulting and Clinical Psychology,* 69 (6), 875-899. doi: 10.1037//0022-006X.69.6.875

Wilson, G.T. (1996). Manual-based treatments: The clinical application of research findings. *Behaviour Research and Therapy, 34(4),* 295-314. doi: 10.1016/0005-7967(95)00084-4

World Health Organization (2012). *Psychoeducation, family interventions and cognitive-behavioural therapy.* Geneva: World Health Organization.

Wykes, T., Steel, C., Everitt, B., & Tarrier, N. (2008). Cognitive behavior therapy for schizophrenia: Effect sizes, clinical models, and methodological rigor. *Schizophrenia Bulletin, 34,* 523-537. doi: 10.1093/schbul/sbm114

Yung, A., & McGorry, P. (1996). The prodromal phase of first-episode psychosis: Past and current conceptualizations. *Schizophrenia Bulletin, 22(2),* 353-370. doi: 10.1093/schbul/22.2.353

Zhong, N., Yuan, Y., Chen, H., (...), Hao, W., & Zhao, M. (2015). Effects of a randomized comprehensive psychosocial intervention based on cognitive behavioral therapy theory and motivational interviewing techniques for community rehabilitation of patients with opioid use disorders in Shanghai, China. *Journal of Addiction Medicine, 9 (4),* 322-330. doi: 10.1097/ADM.0000000000000139

Zimmermann, G., Favrod, J., Trieu, V. H., & Pomini, V. (2005). The effect of cognitive behavioral treatment on the positive symptoms of schizophrenia spectrum disorders: A meta-analysis. *Schizophrenia Research, 77*(1), 1-9. doi: 10.1016/j.schres.2005.02.018

Zubin, J., & Spring, B. (1977). Vulnerability: A new view of schizophrenia. *Journal of Abnormal Psychology, 86,* 103-126. doi: 10.1037/0021-843X.86.2.103

Appendices

Appendix A

DSM 5 criteria for schizophrenia

Table 1.

DSM-5 criteria for schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1 -month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
1. Delusions.
2. Hallucinations.
3. Disorganized speech (e.g., frequent derailment or incoherence).
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms (i.e., diminished emotional expression or avolition).
B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).
C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Cri- terion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.
F. If there is a history of autism spectrum disorder or a communication disorder of child- hood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Appendix B

Psychological interventions for psychosis

1 Establishing a therapeutic alliance and collaborative formulation.

The development of a strong alliance is paramount in this population, given individuals often have difficulties with paranoia and intrusive or commanding voices (Sivec & Montesano, 2012). It is understood that this relationship may take time (Rector & Beck, 2001), but it is important for individuals to feel they can discuss their symptoms without judgment or fear of hospitalization (Sivec & Montesano, 2012). This allows the therapist to get a good understanding of their current symptoms and concerns, and possible beliefs driving these (Fowler et al, 1995). A normalizing rationale is also a key ingredient to CBT for psychosis (Fowler et al, 1995; Rector & Beck, 2001), helping the individual understand that their experiences are not uncommon and are also experienced by those without schizophrenia, such as those with sleep deprivation, loss or trauma (Sivec & Montesano, 2012). This will pave the way for psychoeducation.

2 Psychoeducation

The stress-vulnerability model (Zubin & Spring, 1979) is often used to describe symptom onset, using the individual's experiences rather than didactic learning (Fowler et al, 1995). A study examining the techniques used in the study by Sensky and colleagues (2000) determined that those considered 'responders' to treatment were those who received sound psychoeducation, and a normalizing experience including self-disclosure from the therapist (Dudley et al, 2007).

3 Coping Strategies

This is often a first step for individuals, either because trust needs to be built over time before beliefs are challenged cognitively or behaviourally, or because

individuals are very fixed in their beliefs and cannot entertain an alternative view (Tarrier, 2008). Most commonly this involves distraction of attention techniques, including listening to music, or increasing/changing activity (Sivec & Montesano,2012; Tarrier, 2008).

4 Cognitive Strategies

Techniques are focused on the individual's perceived problems and symptoms as part of a collaborative case formulation (Fowler et al, 1995). Common strategies include awareness training, attention switching, modifying beliefs and self-statements and reattribution of experiences (Tarrier, 2008). Common themes of cognitions that are targeted include threat of harm, loss of control, isolation and perceived defectiveness or worthlessness (Close & Schuller, 2004). Most treatments include a focus on changing or altering delusional beliefs and beliefs about hallucinations (Fowler et al, 1995;Sivec & Montesano, 2012; Tarrier, 2008). Techniques to reattribute or shift thoughts or beliefs are common to all CBT methods, and include tallying evidence for and against, using pie charts to explore the likelihood of alternative beliefs, the continuum task and behavioural experiments (Morrison et al, 2004).

5 Behavioural Strategies

Behavioural components of CBT for schizophrenia typically include behavioural activation to improve negative symtpoms (Tarrier, 2008), and behavioural experiments to reality test unhelpful cognitions (Sivec & Montesano, 2012). Common experiments for people with schizophrenia run along themes such as a person's ability to act against the wishes of voices, that if they show weakness or vulnerability they will be attacked by others, that other people hold beliefs about them, and use of public transport (Morrison et al, 2004).

6 Targeting comorbid affective states

Morrison and colleagues recommend that therapists approach other affective states as they would if the person did not have psychosis. That is, with a comprehensive collaborative case formulation, the therapist and individual agree on what difficulties to target together, and evidence-based CBT techniques for depression, anxiety disorders, personality disorders, or substance use disorders are utilized as they would for any other person experiencing those difficulties (Morrison et al, 2004).

7 Relapse Prevention

Relapse prevention often follows a typical course: identifying triggers and identifying strategies that can be utilized to target that stressor/trigger (Morrison et al, 2004). Many packages have been developed around this, including the Wellness Recovery Action Plan described by Mary Copeland (1997) which details the development of a wellness ‘toolbox’, giving the individual an understanding of what keeps them well, and what changes they notice when they become unwell. It then guides them through identifying daily maintenance for keeping well, triggers, early warning signs, when things are breaking down and a crisis plan, as well as post crisis planning.

Appendix C

Checklist of important components of CBT for schizophrenia

- Normalising Symptoms
- Psychoeducation and engagement
- Cognitive Component (restructuring or behavioural experiments)
- Behavioural Component (exposure, behavioural activation)
- Address positive and/or negative symptoms in treatment
- Address other symptoms (anxiety/depression)
- Homework assigned
- Manualised/Structured
- At least weekly sessions
- Problem Solving Skills component
- Social Skills component
- Coping Skills component
- Medication Adherence module
- Repeated measure of symptoms (more than pre-post measures)
- Relapse prevention component
- CBT trained clinician delivering intervention
- Therapist that is trained/experienced in treatment of psychosis
- Supervision provided for therapists
- Risk Management specified

Score ___ (out of 20).